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ABSTRACT

This document contains the prepared statements and panel testimony from the Congressional hearing on over-the-counter (OTC) drug use by the elderly. Opening statements are given by Representatives Claude Pepper (chairman), Ralph Regula, Mary Rose Oakar, Michael Bilirakis, Tom Lantos, and Hal Daub. Topics which are covered include the incidence and quantity of drug use by the elderly, health risks, adverse reactions, phenylpropanolamine (PPA), consumer protection, and the Federal Drug Administration's (FDA) role in the OTC drug safety and regulation. Testimony of the first panel on OTC drugs, particularly weight reduction medications containing PPA, is given by representatives of the Health Research Group, the National Broadcasting Company, and consumers. Testimony of the second panel on mail fraud schemes perpetrated against senior citizens is given by consumer advocates representing the United States Postal Service, Criminal Investigations and Consumer Protection Divisions, and the Center for Science in the Public Interest. Testimony of the third panel on evaluating the safety and efficacy of various drugs including PPA is given by medical experts from Georgetown, Indiana, Johns Hopkins, and George Washington Universities. Testimony of the fourth and final panel on the safety and efficacy of PPA is given by industry officials from the Thompson Medical Company, Inc., representing the fields of pharmacy, cardiology, sociology, psychology, and medicine. The three appendices contain additional material on medication use/abuse among the Pinellas County, Florida elderly, the FDA list of adverse drug reactions to PPA, the Washington State Board of Pharmacy review of OTC drugs, and prepared statements of panel representatives. (BL)

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ED245148

SAFETY AND EFFICACY OF OVER-THE-COUNTER DRUG USE BY THE ELDERLY

HEARING

BEFORE THE

SUBCOMMITTEE ON
HEALTH AND LONG-TERM CARE

OF THE

SELECT COMMITTEE ON AGING
HOUSE OF REPRESENTATIVES

NINETY-EIGHTH CONGRESS

FIRST SESSION

JULY 21, 1983

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SAFETY AND EFFICACY OF OVER-THE-COUNTER DRUG USE BY THE ELDERLY

THURSDAY, JULY 21, 1983

House of Representatives,
Select Committee on Aging,
Subcommittee on Health and Long-Term Care,
Washington, D.C.

The subcommittee met, pursuant to notice, at 9 a.m., in room 2247, Rayburn House Office Building, Hon. Claude Pepper (chairman of the subcommittee) presiding.

Members present: Representatives Pepper of Florida, Oakar of Ohio, Ferraro of New York, Lantos of California, Regula of New Jersey, Wortley of New York, Daub of Nebraska, and Bilirakis of Florida.

Staff present: Bill Halamandaris, staff director; Kathleen G. Cravedi, assistant staff director; Kitty Edwards, staff assistant; Bonnie Hogue, intern; Peter Reineck, intern; Andi Samuels, intern; James Oberle, Ph. D., minority staff director; and Susan Roland, minority staff assistant, of the Subcommittee on Health and Long-Term Care; Mildred Vinicor, special assistant; Bruce Fried, press secretary; Nancy Lea Mond, administrative assistant; and Don Rosenblum, intern, of Representative Oakar's staff.

OPENING STATEMENT OF CHAIRMAN CLAUDE PEPPER

Mr. **Pepper**. The committee will come to order, please.

I am pleased to see my colleagues here this morning and so many of you in the audience interested in a subject which we regard as very critical; namely, the use of over-the-counter drugs. You remember recently we discussed the question of prescription drugs and the hazards and injuries sustained by the elderly people of this country from the use of prescription drugs. Now those, of course, are prescribed by registered, qualified doctors.

Now, we are today dealing with drugs that are sold in the drugstores and in public markets. I want to commend one of our very distinguished members, Ms. Mary Rose Oakar. She initiated the suggestion that we have a hearing upon this subject.

So, we are very pleased to be considering this matter.

Several weeks ago, as I said, we joined the Senate Special Committee on Aging in examining drug misuse among the elderly. You know, people over 65 constitute about 11 percent of the population of the country. And yet they consume about a third of the drugs that are prescribed. We know that, on the average, each elderly person consumes or takes about 13 prescription drugs a year.

Now then, we've discovered about the extent to which the elderly people buy these over-the-counter drugs. So, not only do about 11 percent of the Nation's population consume about a third of the prescription drugs, but by the year 2000 our elderly number will be about 33 million persons and we will consume about 50 percent of all the prescription drugs annually.

It's rather shocking to think that drugs, which are supposed to be taken against illness, against disease, may also be a source of illness to elderly people. The estimated national cost of drug-induced hospitalization is close to $21 billion a year.

Our joint hearing focused primarily, as I said, on the problem surrounding the use of prescription drugs, and the subject of today's hearing, over-the-counter drugs, or nonprescription drugs, were only incidentally discussed. Yet, nonprescription drugs account for at least 40 percent of all the drugs that are used by elderly people. That is, of all the drugs elderly people use, about 40 percent of them are over-the-counter drugs.

They are combined with an average of 13 prescription drugs that the elderly person takes per year. You can see the amount of drugs that are being consumed by the elderly people of the country alone.

Our subcommittee has discovered that Americans spend about $10 billion each year on more than 300,000 over-the-counter drugs available in the United States. And we find, we regret to say, from $3 billion to $4 billion of that amount is wasted on products with ingredients lacking evidence of safety or efficacy according to evidence that our subcommittee has received. In other words, it's a waste of that amount of money paid by the elderly.

This is particularly disturbing in light of the fact that elderly people commonly purchase over-the-counter drugs. In fact, about 70 percent, in our figures, of the elderly people buy these over-the-counter drugs.

In the last Congress we asked the Postmaster General to undertake a massive investigation of drugs that are bought by the elderly people through the mail. At an early date we expect the publication of that report by the Postal Service, which will reveal some very, very interesting—indeed, some shocking—information. We find that one of the ingredients commonly or often found in these drugs that the elderly take is the substance called PPA. That drug is contained in a great many different things that the elderly purchase.

For example, they are contained in St. Joseph's cold tablets, Contac capsules, Ayds Weight Suppressant, Alka-Seltzer Plus cold medicine, and diet products Dexatrim, Diadex, Ordinex, among many others. Now, this PPA is one of the popular ingredients in most drugs, at least a great many of them. It has come to be about the fourth most numerous ingredient used in the drugs including prescription drugs.

These are the symptoms that generally are associated with the use of these PPA or in drugs where PPA is an ingredient in it. These symptoms include insomnia, nervousness, seizures, severe headaches, and psychosis, as well as elevated cardiac enzymes, hypertension, and cerebral hemorrhage, and in some cases death.

The risk associated with the use of over-the-counter drugs in weight reduction products containing PPA are particularly acute.

According to the Food and Drug Administration, three-fourths of the emergency room visits related to PPA use between 1978 and 1981 involved over-the-counter products.

The National Clearinghouse for Poison Control Centers quantified these 3 actions reporting 10,000 PPA poisonings last year, at least 1,000 of which resulted in emergency room treatment. In spite of numerous scientific studies and medical evidence which documents that PPA causes an elevation in blood pressure, the FDA, the agency with responsibility for reviewing the over-the-counter drugs for safety and effectiveness, has taken little action except to conclude that further study is necessary.

I was on the "Today Show" this morning and one of the questions asked was the people that put these drugs out say "But the warnings, the warnings are on the labels, don't use except according to directions." Well, I said, it's just about the same as an insurance policy. People just don't read the fine print. Ms. O'Reilley here was on the program with me this morning and she will be testifying later on this matter.

But we all know that the elderly people, a lot of times, forget about their prescriptions, they forget about what the directions are even for their prescribed drugs. They get mixed up on it. A man called me in Miami not long ago, frantically and said, "My doctor is out of town and I don't know how to take my medicine." Well, he didn't know how to read his prescriptions that are on the drugs that had been prescribed by the doctor, let alone read all that fine print on these labels on a lot of these things.

So, it seems to me that the FDA ought to not just rely on people protecting themselves. We know how we generally buy these over-the-counter drugs. We hear somebody say that it's a good thing to take or we've heard of somebody else taking it with satisfaction and we say, "Well, I believe I'll try," and we don't read all these little fine print warnings that are on there. It seems to me the FDA should protect the public against anything that is potentially harmful to them.

Well, in the meantime the 4 million Americans who regularly buy products containing PPA remain at risk. Obviously for older Americans who already take numerous medications and suffer from hypertension or other heart problems, their risk is much greater. You see, the warning may be on there, that little fine print, and it may say if you've got heart problems don't take this, but they don't read that. They just take it. It says it's for weight reduction or this, that, or the other, and they go right on and take it.

The Postal Service will tell us how the diet drugs they purchased can be obtained by anyone, either over the counter or through the mails, without regard to the health status of the purchaser. Medical opinions obtained on these diet drugs revealed they do little to control weight and are especially dangerous if taken by senior citizens.

One of the things that most people don't realize is that since, as I said, the elderly people have about 13 prescription drugs on an annual basis that they take, now then, when you go add that they take—that 40 percent of all the drugs they take are over-the-counter, they don't anticipate the sometimes hurtful, harmful, interraction among these drugs. And you can't read anything about that on the label, and so people just ought not take dangerous drugs, or be allowed access to them, it seems to me. It may be very dangerous to them.

So today we will hear from those who purchase these drugs and suffer adverse drug reactions. We will hear from a number of well-known consumer advocates who will reveal the findings of their own investigations of over-the-counter drugs. We will hear from medical experts who will tell us what risks are involved in the use of over-the-counter drugs. We will hear from the Food and Drug Administration who will respond to our concerns regarding their reports to monitor adverse reactions to over-the-counter medications. And we will hear from industry representatives who will detail for us their views on these important issues. So, we look forward to hearing these important witnesses this morning on this very important subject.

[The prepared statement of Chairman Pepper follows:]

PREPARED STATEMENT OF CHAIRMAN CLAUDE PEPPER

Ladies and gentlemen. Members of the subcommittee. Today we are convening a hearing to examine the safety and efficacy of over-the-counter drug usage among the elderly. My distinguished colleague from Ohio, Congresswoman Mary Rose Oakar, requested this hearing by the subcommittee—and, I was honored to grant that request and to comment briefly on this important national issue.

Several weeks ago, we joined the Senate Special Committee on Aging in examining drug misuse among the elderly. We found that the problem of drug misuse among older Americans is particularly alarming in light of certain demographic trends:

Today, older Americans represent 11 percent of the Nation's population, yet they consume about one-third of the 1.5 billion prescriptions written annually; on the average, elderly take 13 prescriptions a year;

By the year 2000, our elderly will number about 33 million persons, and consume about 50 percent of all prescription drugs annually;

Elderly are twice as likely to be seen in hospital emergency rooms as those under age 60; and, when reactions occur the hospital stay is doubled;

The estimated national cost of drug-induced hospitalization is close to $21 billion annually;

Our joint hearing focused primarily on the problems surrounding the use of prescription drugs—and the subject of today's hearing "Over-the-Counter (OTC) Drugs, or Non-Prescription Drugs" were only incidentally discussed. Yet, non-prescription drugs account for at least 40 percent of all drugs used by the elderly, and when they are combined with the 13 prescription drugs an average senior consumes annually—the side effects and adverse reactions become even more unpredictable.

My subcommittee has discovered that Americans spend about $10 billion each year on the more than 300,000 OTC medications available in the United States today. As much as $3 to $4 billion are wasted on products with ingredients lacking evidence of safety or efficacy, according to evidence reviewed by the subcommittee. This is particularly disturbing in light of the fact that elderly commonly purchase OTC drugs—almost 70 percent of the elderly use such medications, as compared with 10 percent of the general adult population.

Last Congress, I asked the U.S. Postmaster General to join my committee in undertaking a massive investigation into frauds perpetrated through the U.S. mails. One fact of that investigation attempted to determine what senior citizens get when they purchase drugs through the mail. The Postal Service will release a portion of our findings in that investigation—specifically as they relate to non-prescription diet drugs which contain a substance called "PPA."

Consider the following facts regarding PPA:

According to the FDA, over 700 prescription products contain PPA; It is ranked sixth among the top ten generic substances contained in all drugs; when OTC medications containing PPA are added—it becomes the fourth most commonly used generic substance in all drugs;

Nearly 4 million Americans consumed 10 billion doses of products containing PPA last year. Every household medicine cabinet probably includes one product containing PPA;

Among the hundreds of OTC products containing PPA are: St. Joseph's cold tablets, Contac capsules, Ayds weight suppressant; Alka Seltzer Plus cold medicine, and diet products Dexatrim, Diadex, Ordinex, among numerous others;

The following adverse reactions associated with PPA, according to FDA files, include: insomnia, nervousness, seizures, severe headaches, and psychosis, as well as elevated cardiac enzymes, hypertension and cerebral hemorrage and death;

The risks associated with the use of OTC and weight reduction products containing PPA are particularly acute. According to the FDA three-fourths of the emergency room visits related to PPA use between 1978 and 1981 involved OTC products; The National Clearinghouse for Poison Control Centers quantified these reactions, reporting 10,000 PPA poisonings last year—at least 1,000 resulted in emergency room treatment.

In spite of numerous scientific studies and medical evidence which documents that PPA causes an elevation in blood pressure, the FDA—the agency with responsibility for reviewing OTC drugs for safety and effectiveness—has taken little action except to conclude that further studies are necessary. In the meantime, the 4 million Americans who regularly buy products containing PPA remain at risk. Obviously, for older Americans who already take numerous medications and suffer from hypertension and other heart problems—their risk is much greater.

The Postal Service will tell us how the diet drugs they purchased can be obtained by anyone either over-the-counter or through the mails without regard to the health status of the purchaser. Medical opinions obtained on these diet drugs revealed they do little to control weight and are especially dangerous if taken by senior citizens.

Today, we will hear from those who purchased these drugs and suffered adverse drug reactions; we will hear from a number of well known consumer advocates who will reveal the findings of their own investigations of OTC drugs; we will hear from medical experts who will tell us what risks are involved in the use of OTC drugs; we will hear from the Food and Drug Administration—who will respond to our concerns regarding their efforts to monitor adverse reactions to OTC medications; and we will hear from industry representatives who will detail for us their views on this important issue.

I look forward to hear the testimony and learning what the Congress might do to help curb the incidence of drug misuse among older Americans.

Thank you.

Mr. Pepper. Mr. Regula?

STATEMENT OF REPRESENTATIVE RALPH REGULA

Mr. Regula. Thank you, Mr. Chairman. First of all, I want to compliment you on having this hearing. I think it's very important that we examine this topic. Ponce de Leon looked for the magic fountain and I think there's always a temptation in the modern world, with the tremendous advertising budgets, that people look for the magic drug or the magic pill that somehow will cure all ills, and, therefore, it's important that we examine this problem as it impacts on the elderly.

I would like unanimous consent to make my statement a part of the record.

Mr. Pepper. Without objection, it will be so ordered.

[The prepared statement of Representative Regula follows:]

Prepared Statement of Representative Ralph S. Regula

Mr. Chairman, I want to thank you for holding this hearing today. Not long ago our subcommittee joined with the Senate's Special Committee on Aging to investigate and discuss the problems people, especially the elderly, face with prescription drugs. At that time I was shocked to discover that the elderly, which comprise approximately 11.4 percent of our population, consume nearly one third of all prescription drugs in the United States. Additionally, they average, in consumption, 13 prescription drugs per year. At the same, Mr. Chairman, we were made vividly aware of the tremendous lack of knowledge in the area of how one medication interacts with another medication. In relation to our elderly we are talking of not just two or three drugs which must interact, but an average of 13 different drugs which must interact.

To make matters worse, the tests which are conducted to determine the efficacy and safety of these drugs are conducted, in the final stages, with persons, generally male, of good health between the ages of 25 and 35. Now I am not a medical researcher but I think I can safely say that the metabolism of a young male in good health and the metabolism of an individual over the age of 60 or 65, many of which are women, differ greatly.

This is why I believe these hearings are vital to the well-being of our senior citizens whose numbers will more than double to nearly 23 percent of the population by the year 2025. Their health and their lives, Mr. Chairman, depend on the knowledge of drug interaction which we now lack. But this is only one part of the problem we face.

We are here today to investigate the second part of this problem: over-the-counter drugs (OTC). It is difficult to gain an accurate figure of the elderly's use of over-the-counter drugs because these are not required to be logged in as they are sold. However, it is estimated that the elderly consume approximately the same percentage (one third), if not more, of all OTC sold in the United States as they do of prescription drugs. Unfortunately, we lack the same knowledge needed for OTC as we do for prescription drugs.

Add this 33 percent of all OTC with the average of 13 prescription drugs the elderly consume per year with the lack of knowledge we have on drug interaction; the lack of tests and studies as to how even one drug affects the metabolism of the over age 65 group as opposed to the young healthy males; the fact that many times the patient is not fully aware of how or when to take their medication; what not to mix with other medications; and the fact that many patients are too intimidated to insist that their physician sit down with them to discuss all the ins and outs of their illness and the medications given to cure that illness, and we now have a definite life threatening situation.

Something must be done to correct these problems. We must make the public more aware of the dangers of mixing medication, both prescription and over-the-counter drugs. Additionally, we must make the medical community aware of their reponsibility to their patients to inform them of exactly what medications they are taking, of what over-the-counter drugs the patients should not use in conjunction with their prescriptions and that above all they should first investigate the patients' medication history to discover what, if any, other medication the patient has or is taking. As you remember, we were informed at our joint hearing with the Senate, this history is not always done now. Finally, and most importantly we should make sure that the drugs which are being tested include tests to discover the ramifications of the elderly's consumption of those drugs.

I hope this hearing will accomplish an increased awareness in the public, medical community, pharmaceutical companies producing these drugs, and the FDA which oversees the governing aspects of the sale of these drugs.

Thank you Mr. Chairman.

Mr. REGULA. Just a couple of comments. One of the important reasons for a hearing of this type is a recognition of the different ways drugs impact on people, particularly in relationship to age. The elderly metabolize drugs somewhat differently than a younger person and therefore a drug would have a different impact on that individual.

Second, as you point out, Mr. Chairman, there is the interreaction of the prescription with nonprescription drugs and, of course, just the sheer volume of drugs creates a problem if taken in any sizable quantities and at the same time.

Third, I think there is a temptation to use nonprescription drugs because of the savings in cost. It's expensive to get a prescription; it involves a visit to a physician usually, or some type of a medical service. The temptation would be, and particularly with the power of advertising, to say that I'll find that magic drug that will solve the problems without any great cost. I think having a hearing of this type will certainly focus attention on the problem and make us all more aware of it and perhaps, as a result of our findings from this and other hearings, we can make recommendations to the appropriate committees for more effective control. Also, the appropriate agencies will be sensitized to the problem.

Mr. PEPPER. Thank you very much, Mr. Regula.

Now, as I said, the lady that suggested that we have this hearing on this subject was Mary Rose Oakar. We are pleased to have her give her opening statement.

STATEMENT OF REPRESENTATIVE MARY ROSE OAKAR

Ms. OAKAR. Thank you, Mr. Chairman. Thank you for the leadership you have provided on this issue and for the courage you've demonstrated in having this hearing. There has been a tremendous amount of pressure placed on you as Chair and your staff and my staff and others, not to have this hearing. I'm very proud of you, Mr. Chairman, and your concern for the consumer.

We are not here to indict the entire drug industry. We realize that they have made significant contributions to the American public and we want to make that very, very clear.

What we are here to say, though, today, at least this member, is that the drug industry for Americans, is a $25 billion industry; and, with respect to the elderly population, 20 percent of their expenses for health care go to over-the-counter drugs. And that's the subject of our hearing today.

More than 70 percent of the elderly rely on over-the-counter drugs as opposed to 10 percent of a more youthful population. And specifically, when you're talking about the diet pill over-the-counter industry, we know that this is a huge industry. And we know that people spend about $200 million a year on over-the-counter pills, and pills that they buy in the mail, et cetera. We know that there are 10 million people who are buying these pills, most of whom happen to be women.

You know, the advertising is always geared toward women, and some of us feel that it's a certain degree of exploitation.

I'm concerned that, Mr. Chairman, in the invitations that were sent out, the FDA, at least at this moment, did not respond. We did contact Secretary Heckler last night and asked her if she could possibly send somebody. They have declined to be here, when some of the issues really relate to them. Also, the proprietary association that was so concerned about this hearing and harassed my staff so much about this hearing, declined to come today. It is the umbrella organization for the drug industry.

And really, I think it's important to have their point of view.

Mr. Chairman, one of the problems lies in the fact that with respect to over-the-counter drugs there is no mandated reporting when it comes to adverse reactions to FDA. The FDA was supposed to be looking into over-the-counter drugs. With respect to this drug, specifically, let me just give you this as an example, and there are hundreds of others just like this. PPA was on the market before we passed the Food and Drug Administration Act. As a result it was not monitored and was exempted from any kind of attempts to monitor and scrutinize, since it came out in 1937 before the act was passed in 1938, there was no mandated scrutiny. So, PPA was exempted.

Then they required premarket proof for the effectiveness of drugs in 1962. In 1972 the FDA said, "Well, we will review over-the-counter drugs that escaped pre-market safety and effectiveness requirements." Finally, in 1975, FDA got around to having an advisory panel that would look at PPA and other types of miscellaneous drugs, and, finally, an advisory panel did finish its report 4 years later, in 1979, in terms of reviewing PPA. The panel gave that report to the FDA. While they have published some interesting observations in the Federal Register, some of which appear to be contradictory to me, in 1983 they still have not, in any way, shape, or form mandated any kind of requirements with respect to this drug.

How did I get interested in this? I got interested in this because my constituents were affected adversely. A young girl experienced psychotic behavior and had psychiatric treatment. She was an obese young lady, 18 years old. We were very aware of her case and very concerned about it. We found out that while she was taking these pills for dietary purposes, her friends were popping these pills to get a little high. It was kind of a substitute for illegal drugs at a high school level.

So, that was a youthful case. Then we got a call from another individual who was an older American, a woman who was 58 years old, who indicated, and whose children indicated, that her doctor felt she had gotten a stroke by taking over-the-counter diet drugs. So we decided to pursue this and found out that, indeed, there were some consumer advocates who had done some excellent studies of this. Also, we realized that there were hundreds, if not thousands, or millions of people who have experienced tremendous adverse reaction from this type of over-the-counter drug. Furthermore, we realize that PPA has not experienced the scrutiny by FDA that it should have had, that the FDA has dragged its feet with respect to this drug. It's as if they hold up their hands and don't really care about the American public and the reaction to this kind of drug.

Mr. Chairman, I have introduced a bill today that, hopefully, will plug up some of the problems with respect to the FDA. If FDA is not going to use its discretionary authority, then we have to force them to use the power. So we have mandated and required that adverse reactions to over-the-counter drugs be reported not only to FDA, but to this Congress. And there are other areas in the bill.

With your permission, Mr. Chairman, I would like to submit my written statement along with a summary of the legislation that I plan to introduce today, "The Safe and Effective Drug Act of 1983." In addition, I would also like to submit for the hearing record a series of six articles by Judy Grande which appeared in the Cleveland Plain Dealer last week. This excellent series examined the FDA and its regulation of the drug industry in great detail. An 8 month investigation by Ms. Grande brought her to the conclusion that the national system that is supposed to protect the public from unsafe drugs does not work. Her series examines the relationship between FDA and the pharmaceutical industry, deficiencies in clinical testing procedures, and the role of Congress and the Reagan administration. Anyone with a genuine concern for the health and safety of the American public ought to take the time to read this series.

Mr. PEPPER. Without objection, the material will be received.

[The material submitted by Representative Oakar follows:]

PREPARED STATEMENT OF REPRESENTATIVE MARY ROSE OAKAR

I want to thank Chairman Pepper and the Subcommittee on Health and Long-term Care for holding this hearing on the safety and efficacy of over-the-counter drugs. Today's hearing is an important followup to our joint hearing with the Senate Special Committee on Aging on June 28th. In the course of that hearing, I raised some serious concerns about the performance of the Food and Drug Administration in protecting the public from unsafe and ineffective drugs. Although the June 28th hearing focussed on prescription drugs, I made it clear then that my concern covered over-the-counter medication as well. I think that as part of the Subcommittee's series of hearings on "the Crisis in Health Care," it is appropriate that we broaden our focus to include these medicines which represent about 40 percent of the drugs used by the elderly.

In the June 28th hearing we discussed drug interactions that result when an elderly person is taking multiple medications, sometimes under the supervision of two or more physicians. The potential for such interactions is multiplied when OTC drugs are utilized by an elder person already taking several prescription drugs. We would not expect the average older American or, for that matter, any consumer to know that even such a common OTC drug as aspirin can interact dangerously with many prescription medications. An additional source of concern is the fact that elderly Americans are more susceptible than any segment of the populations to the so-called "hidden disease"—high blood pressure and diabetes. 70 percent of people with serious high blood pressure are either completely unaware of it or receive inadequate treatment. 45 percent of the 11 million diabetics in this country are undiagnosed. When one considers the easy availability of OTC's and the lack of consumer awareness about potential interactions, the implications for our elderly citizens are truly frightening.

There are currently about 300,000 OTC drugs available in the United States. Retail sales are estimated at $5.2 billion annually. We are all aware of the wide availability of these drugs. They are sold everywhere, and not only in the corner drugstore: the neighborhood supermarket is likely to have just as wide a selection of OTC products as the local pharmacy. Most Americans assume that drugs they can buy so easily and relatively cheaply must be rather benign. Unfortunately, the average consumer is the victim of a prime example of "circular logic." "They must be harmless: that's why they're over-the-counter!" Both FDA officials and drug manufacturers who should know better subscribe to the same dubious reasoning: they are OTC's because they are harmless; they are harmless because they are OTC's. The truth is that these drugs are largely unregulated, and many OTC products have been on the market for decades without ever being proved safe and effective. They have gone through no pre-marketing approval process, yet they are available to every segment of the population, often in a setting where no qualified pharmacist is available to give advice. How did this incredible situation come about?

In 1938, the Food Drug and Cosmetic Act provided for the first time a comprehensive system for regulating the sale of drugs. The Act required a license for all drugs introduced after that date unless the drug was "generally recognized as safe." It also empowered the FDA to remove from the market any unlicensed drugs introduced after 1938 which were not generally recognized as safe (GRAS). In 1962, Congress adopted the Harris-Kefauver Amendments, which required that drugs also be proven effective for their intended uses. The need for the 1962 Amendments, and this is a key point, was documented by testimony presented at Congressional hearings that the use of safe but ineffective drugs may not only be a waste of consumers' money, but also may be positively injurious to the public's health, since the use of any drug entails certain, unknown risks.

Both the original FDC Act and the 1962 amendments contain "grandfather" clauses which exempt drugs on the market at the time the statutes were enacted from the GRAS/E requirement. Thus, unless they are generally recognized by experts as safe and effective, most, if not virtually all, OTC drugs can not legally be sold. One way of assuring that OTC drugs meet this criterion would be for them to go through the "new drug application" (NDA) process. However, very few manufacturers of OTC drugs have taken this route. Therefore, the vast majority of OTC drugs marketed today are being sold on the basis of their manufacturers' claims that they are GRAS/E. How has the FDA responded to this situation?

In 1966, the FDA began investigating the extent to which OTC drugs met the new efficacy requirements. The agency appointed the National Academy of Sciences—National Research Council to review approximately 420 OTC drugs which were "broadly representative of the whole range of the OTC market." Reporting in 1969, the NAS-NRC concluded that only 25 percent of those drugs were effective for even one use. Not surprisingly, this finding gave the FDA "cause for concern" about OTC drugs in general.

It took until 1972, 10 years after the efficacy amendments were passed, for the FDA to begin a systematic review of all OTC drugs. At that point, the agency realized that there were two possible ways it could proceed to bring OTC drugs into compliance with the law. First, it could bring enforcement actions in federal court against individual products. This approach, it was estimated, would place an "enormous burden" on the agency, since there are around 300,000 OTC brands on the market. A second approach would be to proceed by administrative rulemaking, considering the efficacy of particular ingredients found on OTC drugs. This was deemed a more reasonable way of tackling the task because the agency estimated that there were only 200 active ingredients used in all OTC products. (The number turned out to be considerably more; thus far, the FDA has reviewed 731 active ingredients).

FDA adopted a lengthy and multi-stage procedure involving expert scientific advisory panels, several stages of published monographs, and, ultimately, a final order establishing the conditions under which the ingredients of the OTC drugs studies are GRAS/F.

When the FDA began its OTC review in 1972, the agency estimated that the review would require five years to complete. The time required to complete the review was significant because it was made clear at the time and has been reiterated since that while the review was being carried out, no enforcement actions would be brought against ineffective OTC drugs. This policy is set out in the FDA Compliance Policy Guide, and has been repeated in speeches given to other government agencies, and in published textbooks. A 1979 letter from the Chief Counsel of FDA to the Proprietary Association laid out the policy in clearly stated terms:

> The period during which the OTC Review makes its stately (?) progress toward a final monograph is the period during which FDA is formulating its position on that issue. During that period FDA generally will not take regulatory action against a particular OTC product whose ingredient(s) are within the OTC Review pending issuance of a final monograph covering those ingredient(s). FDA will take enforcement action in cases of danger to the public health or fraud. Even where FDA does not, as a matter of policy, take enforcement action, the burden of good faith compliance with the law remains at all times with the companies marketing OTC products.

There are two major problems with this FDA policy: first, the agency is in effect asking a major industry to regulate itself; second, the review process has taken much longer than anticipated. Originally projected to last five years, it has dragged on for eleven years now, and the end is nowhere in sight. In July of 1981, the Director and Deputy Director of the OTC Review agreed that, realistically, the review would probably not be completed until the year 2000. Based on the FDA's past record of meeting milestones and deadlines in the OTC Review, even that might be too optimistic an estimate. The FDA has consistently underestimated the duration of the OTC Review. At present, the FDA has published only six final monographs plus three final orders which cover single ingredients—a total of nine final documents out of a projected total of 85!

All this would not necessarily be cause for concern if all over-the-counter drugs were really as benign as most Americans assume they are. However, the expert scientific panels appointed by FDA have found that 69 percent of all the OTC ingredient reviewed are not generally recognized as safe and effective. According to the monographs published so far, 37 percent lack evidence of effectiveness, 24 percent lack evidence of safety and effectiveness, and 8 percent lack evidence of safety. While the FDA continues its "stately progress" towards completion of the OTC Review, the American public is spending billion of dollars on products that contain ingredients two-thirds of which are either unsafe or ineffective, or lack evidence of safety and efficacy.

Today I will be introducing legislation that will deal with many of the concerns we discussed at the hearing on the 28th. The general purpose of this legislation is to strengthen the authority of FDA to control the use of all drugs—prescription and OTC—which present risks to the public. The bill would put OTC's under post-marketing scruitiny for the first time. Specifically, it will require manufacturers of over-the-counter drugs to report adverse drug reactions to FDA; extend FDA's authority to require manufacturers to do post-marketing surveillance; and grant FDA the authority to restrict drug marketing if adverse reactions develop after the drug has been approved. In addition, the bill will create a National Center for Drug Surveillance within FDA, mandate an annual report to Congress on adverse reaction data and FDA's response to it, and direct the Commissioner to establish a program to encourage physicians, institutional health care providers and consumers to report adverse drug reactions to FDA. Finally, the legislation will FDA subpoena power it may need to obtain important data from drug testers.

A case in point which illustrates serious deficiencies in the OTC Review program is that of phenylpropanolamine or PPA as an ingredient in weight control products. This ingredient has been of particular interest to me since several of my constituents informed me of their concern with PPA-based diet pills. I began researching the issue further and discovered a large and growing body of evidence linking PPA in diet pills with a variety of adverse reactions. In addition, there seemed to be substantial proof of the ineffectiveness of these pills for controlling weight. Further research into the matter gave me reason to believe that 10 million Americans might be using a product with great risks and very few benefits.

At today's hearing, I hope to examine the controversy surrounding PPA, and hopefully arrive at some answers to certain troubling questions: how has this product remained on the market for 45 years without ever being shown to be safe and effective? Is the diet pill industry accepting the "burden of good faith compliance with the law" while FDA completes its review? Are the ten million Americans who use diet pills being misled or does the product work for them? In an effort to get at the answers to some of these questions, we will be hearing today from victims of serious adverse reactions to diet products containing PPA, doctors and scientists with an understanding of the various aspects of the PPA controversy, industry representatives, and FDA officials. I hope that during the hearing we can also grapple with some fundamental questions about FDA's role. Why, after eleven years, has FDA failed to move beyond the proposed monograph stage with a product so widely used and of such dubious value? In general, how can FDA expedite its OTC Review? Should the agency be giving priority in the review to widely used and potentially hazardous ingredients like PPA? Why is it taking so long, and when will it be finished? I look forward to hearing from all our witnesses, and I hope we can begin to resolve some of the questions I have raised.

Let's Protect Our Citizens From Unsafe and Inaffective Drugs

Modern medicine has come a long way since the 1880s. There are over 300,000 over-the-counter medications and 7,000 prescription drugs readily available in the United States. What is frightening, however, is that as much as $4 billion is wasted on some of these products with ingredients that are neither safe nor effective. How is a senior citizen to know what is safe and what is not? Not only do 70 percent of our elderly use OTC drugs, but the average senior citizen takes 13 prescriptions a year and it is a known fact that the elderly are twice as likely to be treated in an emergency room for an adverse drug reaction than a citizen under 60 years of age. Obviously, this is not a problem that extends beyond the senior citizen population; it affects all age groups.

For many years, I have been concerned about the performance of the FDA in the area of drug safety and effectiveness. A 1969 report to FDA by the National Academy of Sciences and the National Research Council concluded that only 25 percent of a representative sample of over-the-counter drugs were effective for even one use. More recently, panels appointed by FDA have found that 69 percent of all over-the-counter ingredients reviewed are not generally recognized as safe and effective.

In 1972 the FDA began a systematic five year study of all over-the-counter (OTC) drugs. Today—11 years later—FDA estimates that the review will not be completed until the year 2000. Meanwhile, under current law, manufacturers are not even required to report adverse drug reactions to the Food and Drug Administration.

This legislation will make the Food and Drug Administration police the public's health. It will mandate that FDA exercise authority that is now discretionary. It will give the agency new powers to require drug manufacturers to report adverse reactions, to subpoena information, and to require full disclosure of all test results, not simply those that support a new drug application.

Specifically, the bill would:

Require manufacturers of over-the-counter drugs to report adverse drug reactions to the FDA. Under the current system, drug manufacturers of OTC drugs are not obligated to report adverse drug reactions—even if they are life-threatening—to the Food and Drug Administration.

Given the FDA the authority to require drug manufacturers to conduct post-marketing surveillance of prescription and over-the-counter drugs and report the findings to FDA. The Food and Drug Administration cannot now require a drug manufacturer to survey physicians or health care institutions even if FDA suspects that there may be a serious problem.

Authorize FDA to restrict the marketing of a drug if adverse reactions develop after the drug has been approved. Although FDA has considerable authority to require further information and tests before a prescription drug is approved, once the drug has been marketed, FDA has little authority to regulate its use. This provision would allow FDA to restrict a drug to practitioners with special training or experience in it use or to practitioners for use in certain facilities.

Grant to FDA the authority to subpoena records from drug companies. FDA must rely on voluntarism and the goodwill of drug companies to provide the information it requests.

Requires investigators of new drugs to report the test results of all studies to FDA.

Establish a program in FDA to encourage physicians, institutional health care providers and consumers to report adverse reactions to the Agency. It is vital that FDA mount an effort for voluntary reporting through such mechanisms as a too-free number or public service media announcements to encourage the reporting of adverse reactions.

Establish a National Center for Drug Surveillance within FDA to monitor reports of adverse drug reactions and ensure FDA action.

Mandate an annual report to Congress on reported adverse drug reactions and the actions FDA has taken in response.

[From the Plain Dealer, July 10, 1983]

FDA Fails To Protect US—Part 1

(By Judy Grande)

Indianapolis.—The heart attack that forced Harrison Pittman to retire from computer programming at age 53 was a hard blow, but not a fatal one.

Pittman had plenty of reason to live—a wife, five children, a nice home—and he worked hard at recovering. He slimmed down, took long, slow walks and swallowed every pill his cardiologist prescribed.

But an irregular heart beat remained a year after the attack, and he was sent to a clinic that was experimenting with a new cardiac drug.

Pittman signed a form in the clinic consenting to take the drug.

Three days later he died—a human guinea pig.

U.S. Food and Drug Administration (FDA) records later revealed that Pittman, identified in clinic files only by patient number and initials "HP," received extremely high dosages. He was warned that test with a similar drug killed humans and laboratory animals.

His is but one of many stories of human experimentation conducted by an industry so cloaked in secrecy and so skilled at self-promotion that it defies most attempts to regulate it.

An eight-month investigation by The Plain Dealer found that the national system that is supposed to protect the public from unsafe drugs does not work. It is failing because:

The physicians hired by the pharmaceutical companies to test experimental drugs—the front line defenders against unsafe drugs—at time endanger lives by departing from approved procedures.

The overburdened, underfinanced FDA often closes its eyes to problems in the pharmaceutical industry because it lacks the skills, the staff or the stamina to do otherwise.

The FDA rules and regulations of the past decade were developed by lawyers with strong ties to the pharmaceutical industry.

The Reagan administration is intent upon dismantling some of the safety mechanisms incorporated in the drug regulation system.

Physicians are no longer the sole targets of ever-growing, at times misleading, promotional campaigns of pharmaceutical firms. Prescription-drug advertising is for the first time being hurled at the American public through television and magazines, creating new problems for the FDA.

Congress has done little to reform drug laws to help the FDA, but it regularly grants favors to the pharmaceutical industry.

Scores of interviews and a detailed review of thousands of pages of federal documents and other reports reveal a pattern of wrongdoing among several major pharmaceutical companies.

Pittman was only one of many who have died nationwide during clinical experiments on newly developed drugs. The exact number of deaths is not available from the FDA.

Some of the deaths may have been inevitable because the patients who volunteered were terminal and viewed the experiments as a last resort. Others, however, may have died needlessly.

For several, death came on the top floor of Wishard Memorial Hospital here, the spanking clean, quiet part of a public hospital that is home to Eli Lilly Clinic.

It is here that experimental drugs developed by Eli Lilly & Co. scientists are tested on human subjects.

It was here that Pittman and others agreed to enter a study on a drug called Drobuline, a compound being tested for treatment of cardiac arrythmias.

And it was here, several years after his death, that patient "HP" became a statistic in an FDA investigation of the drug testing practices of Lilly, one of the world's largest, most profitable pharmaceutical firms.

Pittman died Nov. 21, 1977, three days after entering Lilly Clinic. But, typical of the pace at which the FDA moves, it was not until a year later—after a former Lilly employe complained—that the FDA became aware of problems in the clinic's drug testing programs.

A July 1980 FDA inspection report, released by the house government operations subcommittee on intergovernmental relations and human resources, stated a check of some patient records on Drobuline showed 70 percent had been given the wrong consent forms, which authorize testing and list risks associated with the particular drug.

Patient "HHP" got the wrong papers, a two-paged form intended for healthy volunteers. The first page states, "Compound 112092 (Drobuline) has been given only to animals so that you will be the first subjects to receive this drug." The second page states, "you will receive no benefit from this drug, but you will provide us with information which is necessary for us to have before this drug is given to people with abnormal heartbeats."

Pittman received 400 mg. doses, but after his death others in the program were lowered to doses in the 300-mg range. FDA records show even those levels were higher than the maximum-200 mg, doses originally planned by Lilly and OK'd by the FDA.

A September 1980 memo from an FDA investigator to Dr. Frances O. Kelsey, FDA director of scientific investigations, said his FDA review of the Drobuline trials suggested "a very early, perhaps premature start-up to the patient trials, the occurrence of adverse effects, patient deaths, a return to normal volunteer testing and an early termination of human studies, essentially without explanation."

"In March of 1978," the memo continues, "two events appear to have resulted in an end to Lilly's Drobuline program. Having pushed the dosage of the drug to the limits of the patient's tolerance, and having demonstrated relatively unimpressive efficacy, Lilly now wanted to further increase the dose."

Dr. Michael J. Hensley, the investigator who has since left the FDA, then told of a patient who was released from the hospital on the 10th day of therapy, March 23, 1978 and suffered a fatal heart attack at home three hours later.

"Report of the death to the FDA was not made until April 20, 1978," Hensley wrote, "and at the time it was stated the patient's response to the drug was said to have been excellent and no adverse effects were noted."

The doctor conducting the Drobuline trials was Alfred F. Fasola, a Lilly employe, who had tested a similar drug, Aprindine, which resulted in patient deaths in 1973 and 1974.

In a November 1980 letter to Fasola, Kelsey said, "Information discovered during both the Aprindine and Drobuline inspections leads us to believe that you have repeatedly or deliberately failed to comply with the regulations relating to the proper conduct of a clinical study involving an investigational new drug."

Kelsey cited violations of the Federal drug code by Fasola, including failure to keep track of all the drug received and failure to maintain adequate, accurate case histories.

On Jan. 13, 1981, an informal conference was held at the FDA to consider whether Fasola should be disqualified from participating in new drug studies. More than two years later, the FDA has taken no action on Fasola's case. As of last month he was still working at Lilly. The FDA will not comment on the status of this investigation other than to say it is in abeyance.

Lilly will not comment on any questions related to new drug studies, its clinic or Fasola, citing the continuing investigation as reason for its silence.

Dr. Fasola could not be reached for comment.

The Justice Department is investigating Lilly after the FDA charged that the company withheld information on patient deaths before approval of Oraflex, the anti-arthritis drug pulled off the market last year following reports of deaths in the United States and Great Britain.

Some public statements from the firm have emerged, however.

On Aug. 9, 1982, after a congressional hearing on Oraflex and the drug approval process, Lilly's board chairman, Richard D. Wood, wrote his stockholders. He said charges against Lilly were unsubstantiated and that they were predicated on memoranda prepared by operational-level FDA investigators.

Lilly is not unique in its difficulties with experimental drugs, but it is one of the few companies with its own clinic for human testing—most contract with doctors who specialize in the type of ailment the drug is intended to cure.

The testing procedure is very costly for firms involved and very lucrative for the tester, with many grossing as much as $1 million a year. The procedure has been policed by the FDA for many years with minimal success.

Of 85? inspections of drug studies conducted by the FDA between June 1977 and last February, only 16% of the testing programs checked were found to be in full compliance with the law, according to the FDA Division of Scientific Investigations. Of the deficiencies found, nearly half involved informed consent and 35% involved inadequate drug recordkeeping.

Informed consent problems can include understating the risks of the experimental drug or use of overly positive language on safety and efficacy.

What is most disturbing, said Kelsey, is that inspections are conducted only on those studies selected by the companies as most thorough and favorable to their new drugs.

"If these figures were compiled from the overall thousands of studies, the percentages would be OK. But these are the basic reviewers that the sponsors finger as most reliable," Kelsey said.

Kelsey is a legendary figure at FDA. She received a medal from President John F. Kennedy in 1962 for preventing the marketing in the United States of Thalidomide, a sedative that caused birth defects in the children of European women who used it.

But there is only so much Kelsey and her staff can do. A hodgepodge of FDA-written regulations governing clinical investigations are vague, lenient and cumbersome. And budgets are forever being reduced. Like many other FDA employes, they may fall short of desired goals, not for lack of trying, but lack of time.

In any given three-year period, some 14,000 clinical investigations are involved in drug studies. The FDA can inspect only about 600 studies.

Congress in 1977 gave the FDA the budget authority to increase the division staff to 52. The highest it ever reached was about 40. This fiscal year it was lowered to 32. Kelsey said it would likely be reduced further.

While reducing inspection staff, the FDA, to the delight of drug makers, is adding to the division that reviews new drug applications to speed up marketing approval.

One of the biggest obstacles facing Kelsey's staff is the FDA's lack of clout. Doctors often won't give them records. The FDA has no subpoena power.

The FDA has disqualified 52 clinical investigators from further testing since 1964, and nine others have agreed to some restrictions on using investigational drugs. But the bureaucratic road to disqualification is not short. In the 1960's it took only about six weeks to declare a physician ineligible to test drugs. It now takes as long as four years.

An informal hearing with the FDA commissioner has been replaced with a formal one, requiring participation of legal counsel for the physician and several FDA officials as well.

"Thus we have three sets of FDA attorneys (for the bureau, for the hearing officer and for the commissioner)," said Dr. Alan B. Lisook, chief of the agency's clinical investigations branch, "all of whom are forbidden to speak to one another concerning the case on hand."

The clinical investigator, meanwhile, can continue to study the drug until a final determination is made. The FDA has the authority to immediately stop an investigator from further study by citing a serious hazard to health, but this has happened only once.

That was the case of Dr. Carl E. Blunck of Louisiana, who in 1977 was given permission to receive a drug called Anginin. It was to be for his personal use, not for disbursement to patients, but FDA records show he administered the drug to more than 30 patients and could account for only about 7,000 of more than 20,000 tablets he had received.

Dr. Michael C. Gelfand of Maryland also was cited for keeping inadequate records, and "compromising both the integrity of the data and the safety of the subjects," according to his FDA file.

"Although Dr. Gelfand did not deliberately violate the regulations, the violations were widespread and ongoing. Some of them, such as the failure to keep adequate patient records containing crucial blood pressure and pulse rate data, are inexcusable," reads the September 1981 decision of FDA Commissioner Arthur Hull Hayes Jr.

But Gelfand had an out—Title 21, Part 312 of the Food and Drug Law, which gives the commissioner the right to declare an investigator eligible if adequate assurances are made that the problem will not happen again. Hayes did exactly that.

"I conclude that although you have repeatedly failed to comply with the regulations governing exemptions for investigational new drugs, you have furnished adequate assurance that the conditions for exemption will be met in the future," Hayes wrote Gelfand. "Consequently, I have decided that you will not be disqualified from receiving investigational new drugs."

The FDA has proposed further weakening the so-called IND (investigational new drug) regulations. The proposal, outlined in the June 9 Federal Register, articulates the flexibility available to clinical investigators to modify approved drug protocols without telling the FDA. It allows drug researchers to conduct new experiments on drugs for other uses without getting FDA approval. These would be limited, the notice states, to situations where safety is not an issue and would be designed primarily for researchers in academic institutions who are exploring new uses for marketed drugs.

There is also a gap in the FDA's monitoring of drug experiments. It has yet to publish regulations on sponsors of the studies—the companies that hire the physicians who do the testing.

These regulations, which would make sponsors more responsible for the actions of their investigators, were first proposed in 1977.

A notice in the same June 9 Federal Register said the sponsor regulations would be made final in the coming months, at about the same time as the new regulations governing investigational new drug studies.

FDA OFTEN FINDS ITS HANDS TIED—PART 2

(By Judy Grande)

WASHINGTON.—Dr. Joseph Feldschuh, a cardiologist, is used to seeing people die. Yet there was something especially disturbing about the dealths in 1979 of two heart patients.

Tests taken at the time of death showed unusually high acid levels in their blood—levels high enough to kill even a person with a normal heart.

Two years later, Feldschuh and a New York colleague were satisfied they had found the cause of the acid overdose—a particular brand of epinephrine, Abboject, (otherwise known as adrenalin), injected into the heart during cardiac arrest.

The brand manufactured by Abbott Laboratories contained eight times the acid of similar products, the doctors determined.

They supported their finding with chemical analyses and a telephone survey of 38 doctors who had administered the drug to their patients.

In June 1982, the doctors notified Abbott of their chilling discovery: Of 852 patients in New York City injected with the Abbott brand, no survivor could be found.

The firm reacted swiftly but silently.

It reformulated the product to contain less acid—used to stabilize the drug—but did not notify the U.S. Food and Drug Administration. And, it did not warn doctors and hospitals of the potentially deadly danger.

Not until last January, when a medical journal published the findings by Feldschuh and Raymond Gambino, a professor at Columbia University's College of Physicians and Surgeons, did Abbott recall the high-acid epinephrine.

Abbott still denies its product was harmful, and criticizes the testing methods used by the two doctors. It stands by its decision not to notify the FDA.

Abbott is on solid legal ground. The FDA, the federal agency responsible for keeping unsafe drugs off the market, claimed no jurisdiction. Because the manufacture of epinephrine predates the 1938 Food, Drug and Cosmetic Act, it escapes regulation.

Beyond meeting with company managers to discuss the "voluntary" recall and telling them they used "poor judgment" in keeping the matter quiet, the FDA has done little.

It considers Feldschuh's claim exaggerated and has taken few steps to find out if the product could have caused any deaths.

"The FDA has no regulatory reason to try and reconstruct what may or may not have happened," said FDA spokesman William Grigg.

Besides, said Grigg, the FDA has never received a complaint of this sort before. Because most cardiac arrest patients cannot be saved, doctors have said they might not suspect an additional factor in the death.

"It's such a dramatic charge (the 852 deaths) but it's a moot point," said Grigg. "Is it worth debating something that's been corrected?"

Feldschuh and others think it is.

"If this is the way we're being protected by the agencies, forget it," said Feldschuh, who is studying the new formula. He contends that it, too, may have enough acid to kill.

Though the Abbott-epinephrine episode may be unusual, it is typical of a common affliction—the FDA's inability to keep close tabs on the pharmaceutical industry it is supposed to regulate.

When health hazards occur the FDA is often the last to know.

This happens not only after products are marketed, but during the drug approval process as well—in part because the FDA is understaffed, overworked and in some areas lacks the skills to handle the ever-growing crises that confront it.

As Dr. Peter B. Vaill, author of a 1982 study of the FDA's division of new drug evaluation, said, the bureau works "in an atmosphere of constant distraction, tension and crisis."

Vaill, professor of human systems at George Washington University who was commissioned by the FDA to make the study, listed the "realities of everyday life" in the FDA. To name a few:

Multiple conflicting outside interests with stakes in how the new drug evaluation process is conducted.

Congressional scrutiny.

Constant time pressure to keep approval on schedule.

Decision making responsibility for life and death.

A history of skirmishing with the pharmaceutical industry, the media and various special-interest groups.

Vaill cited "The heavy dependence of this entire system on the nonprofessional secretarial-clerical staff to generate the system's actual, physical output, and the difficulty the professional staff has in seeking and adapting to this strategic fact."

Those words soon came back to haunt the FDA.

In April 1982, the FDA approved the anti-arthritis drug Oraflex. Not long afterwards, physicians were sent warnings from its maker that the drug could cause kidney and liver problems in the elderly. Soon after that, it was withdrawn because more than 70 people died while taking it here and in Great Britain.

Still being debated, nearly a year later, is what the FDA knew about the toxic effects of the drug and when it knew it.

The FDA division that reviews new drugs had a six-month backlog in its mailroom. It is possible, FDA officials concede, that at least two reports of liver failure sat there unopened.

Dr. Robert Temple, FDA acting director of New Drug Evaluation, cited cases of combined liver and kidney damage that the drug's manufacturer, Eli Lilly & Co., reported to the FDA before the drug's approval. "One was contained in the NDA (new drug application), one was provided as a desk copy to the medical reviewer and the other two might well have not been seen by anybody," he said. "They were probably in the document room."

Each of the FDA's six drug evaluation divisions has a document room, where mail sorted from the central receiving office is sent for disbursal to appropriate individuals. "There was at that time a six-month backlog in the document room," said Temple. "It is always difficult to hire people for the document room. They've had their grade knocked down twice. It's a position of considerable responsibility, yet their grade is GS4 or 5 and salaries are low ($11,949 to $17,383)."

Temple, who said the backlog is down to one month and may soon be current because the FDA is paying overtime to get the work done, did not try to defend the lapse. "One cannot argue that keeping things in your document room is good," he said.

The FDA has a more general staffing problem, said Temple. It is often unable to get quality professional staff because "most people go into medicine to take care of patients. This is not exactly what they had in mind."

Yet, Temple said the FDA acted properly, given the information it had when it approved the drug. The FDA did not learn about the large numbers of deaths until last August, four months after approval. Lilly, however, may have known about them sooner, according to the FDA. The Justice Department is investigating whether Lilly withheld that information.

Because of another FDA backlog—in its computerized system for monitoring adverse effects from marketed drugs—it was again among the last to know that a number of people were having fatal or serious allergic reactions to the painkiller Zomax.

In March, Zomax was voluntarily withdrawn from the market because of five deaths associated with its use. In April, a House Government Operations subcommittee held hearings on the withdrawal and severely criticized the FDA's system of post-marketing surveillance.

"Scarcely a week or a day goes by that most of us here in this room and elsewhere across the country do not take some form of medication," said subcommittee chairman Ted Weiss, D-N.Y.

"I regret to report that I find the results of our investigation most disturbing, in that they very strongly indicate fundamental deficiencies in the FDA's drug approval process and adverse reaction monitoring and analysis system."

Robert Eaton, an FDA pharmacist, told the House subcommittee that as late as last February, one month before the drug was withdrawn, the FDA computer system has logged only half of the more than 1,100 cases of allergic reactions to the drug.

"Those reports could have been anywhere through the system," Eaton said.

But perhaps more disturbing is the fact that as much as one year before the withdrawal, some FDA officials were aware of the dangerous allergic reactions, particularly when the drug was used intermittently, as many painkillers are. They met with the manufacturer, the McNeil Pharmaceutical subsidiary of Johnson & Johnson, to discuss sending a warning to physicians about the reactions. The warning about intermittent use was omitted.

At the Zomax hearing, Commissioner Arthur Hull Hayes Jr. called the FDA's system of post-marketing surveillance the best in the world. Hayes said that since coming to the FDA in 1981 he'd made many administrative and regulatory changes to alleviate some of the reporting problems.

Further slowing FDA activity is the fact that employes in all divisions spend a lot of time away from normal duties to answer Freedom of Information Act requests.

The FDA is the second largest recipient of such requests for information, led only by the Department of Defense. In the first quarter of 1983, it logged 8,492 requests, a 4 percent increase over the previous quarter. In 1982, it cost the FDA $4.7 million and took 130 staff-years to process the requests.

Many requests are from pharmaceutical companies seeking information on competitors' activities—or those of their own firm. A lawyer who represents several major drug companies said it is cheaper for industry to file an FOI request on itself than to have one of its employes research the topic.

The situation may worsen if Congress approves a bill requiring the FDA to notify firms before it releases any information about them. The firm would then have the opportunity to object.

Gerald Deighton, staff director of the FDA's Freedom of Information division, said if predisclosure notification goes through Congress, it will cost the FDA close to $4 million more, take an additional 103 staff-years and double the time (it already takes several months) to get responses out.

FDA Is 8 Years Late With Drug Efficacy Report—Part 3

(By Judy Grande)

Washington—Stuffy nose sufferers know it as the "nighttime cold medicine"—NyQuil, the dark green fluid billed as an antihistamine, analgesic, cough suppressant and decongestant all rolled into one.

It's the largest selling over-the-counter cold product in the United States. And it may not work.

A U.S. Food and Drug Administration advisory panel of scientists in 1976 labeled combination products such as NyQuil as lacking evidence of effectiveness because they contained too many ingredients. While the report did not specifically name any combination drug, NyQuil fits that category because it has a combination of four active ingredients, and an alcohol content of 25 percent. One of these ingredients—the nasal decongestant—is also individually listed as possibly ineffective when taken orally.

But seven years after the panel's report was published in the Federal Register—the official document of governmental action—the FDA is still dragging its feet on a final ruling as to whether products like NyQuil are effective, whether they should be reformulated—or removed from the market.

This scenario is repeated with thousands of over-the-counter (OTC) products, all part of a massive, first-time review of their safety and efficacy. Bogged down in 20,000 volumes of information affecting 400,000 products, the FDA is eight years behind schedule and is not likely to complete its review until the year 2000.

The man who developed the sluggish review process is Peter Barton Hutt, chief FDA counsel from 1971 to 1975.

Although the FDA decided in 1966 to remove unsafe and ineffective OTC drugs from the market, the job was not started until 1972. Hutt had arrived by then. He designed a review procedure that allows corporate responses at so many stages of the review that manufacturers can indefinitely swamp the FDA with information about their products.

Hutt learned his trade as a partner in Covington & Burling, one of Washington's most powerful law fims and one that has represented most of the major pharmaceutical companies.

From there he went to FDA, where he joined a long line of FDA counsels trained in food and drug law by the very industry they came to regulate.

"Our lawyers go in and out of government all the time," said Hutt, who resumed his partnership at Covington & Burling in 1975 and represents the Pharmaceutical Manufacturers Association.

In Washington, this is known as "the revolving door"—the back-and-forth of men and women between federal agencies and the firms they regulate.

The FDA studied its own revolving door in 1981, reporting on 297 senior officials who had left FDA the previous year. Of those, 8 percent went to regulated firms or are employed as their consultants. The FDA considers this a low percentage.

But those figures do not include the agency's lawyers. Those numbers are harder to come by. The Plain Dealer found at least a dozen former FDA counsels who now represent the pharmaceutical industry, or did so before their stints at FDA.

Several came from Covington & Burling, as did Hutt. His influence on the FDA and the drug industry appears as pervasive today as it was in the 1970s.

Others include Richard Merrill (with Covington & Burling from 1965 to 1969), FDA general counsel from 1975-1977 and now dean of the University of Virginia law school, and Terry S. Coleman (with Covington & Burling from 1976-1981), current deputy general counsel for regulations at the Department of Health and Human Services, parent agency of the FDA.

Hutt, a skilled orator and convincing debater, views himself as the prime example of the revolving door and makes no apologies for it.

"What many in industry used to say to me was the only difference after I went to government was that they got the same advice, except it appeared in the Federal Register instead of an envelope from Covington & Burling," he said.

But sometimes he finds his firm's influence embarrassing, as he admitted to a colleague recently. A seminar was held a few months ago to train Senate staffers in food and drug law. A panel discussion was planned with representatives of all the major industries regulated by FDA.

The debate was hardly lively. Nearly every lawyer at the table had the same view of regulation—each was from Covington & Burling.

"There is no question Peter Hutt is responsible by and large for the regulatory framework by which the FDA has operated for the past 10 to 15 years," said Thomas Grumbly, who was executive assistant to former FDA Commissioner Donald Kennedy. "His conception of what FDA regulation is about is expansive."

Regulation of the pharmaceutical industry dates to 1906, when Congress passed the Food and Drug Act. It called for protecting the public from hazardous foods, drugs, cosmetics and medical devices.

In 1962, Congress amended that act to require that all drugs be effective as well as safe, but it was not until the 1970s that the FDA commissioners began implementing the efficacy requirements for drugs marketed before 1962.

It was also during the 1970s that the FDA hearing process became more cumbersome, allowing long delays before the agency could take action against a firm or individual.

Few dispute the worthiness of the safety and efficacy reviews Hutt designed, but many, including consumer-oriented health organizations, blame him and other FDA lawyers for much of what troubles the agency today.

Hutt designed the legal process for review of prescription drugs marketed before the 1962 drug efficacy amendments. That, too, is long overdue. Its schedule was set by a federal judge after several consumer health organizations sued the FDA to speed up the review.

While lengthening procedures to give pharmaceutical firms due process in dealing with regulators, Hutt did try to streamline one regulatory area. In 1974, he hired a lawyer to rewrite the FDA's regulations for approving new drugs—the pharmaceutical industry's No. 1 priority.

"His basic philosophy is the regulators would be better off if they were left alone with lawyers. Politicians will screw it up. Leave it to the guys who are the professionals," said one lawyer of Hutt. "He has an elitist view of what public policy is. But he is a formidable opponent."

Dr. Sidney Wolfe, head of the Ralph Nader-founded Health Research Group, puts it more simply: The FDA is caving in to the pressures of the drug companies.

"They started a procedure in 1972 that should have taken four, five or six years," said Wolfe, a graduate of Case Western Reserve University Medical School. "The panels finished their work years ago, in some cases six or seven years ago, so it's all at the level of the FDA."

Hutt blames delay not on his procedures, but the unexpected amount of ingredients that had to be reviewed. He says it is a miracle it is being done as quickly as it is.

Hutt, author of the textbook on food and drug law used in most law schools, defends the revolving door.

"Everything I accomplished at FDA, in the matter of time in which I did, was accomplished because I had spent 12 years in training for the job," said Hutt. "A government that is as complex as this, you have to bring in people who know something about it."

Hutt added that he would never presume upon a friendship at FDA. "That is the reason I never make a phone call or write a letter . . . because that it seems to me is where the public is entitled to be suspicious."

Hutt numbers many at the FDA among his friends, including former commissioner Donald Kennedy.

Perhaps more than anything else, it is these friendships that make industry lawyers so powerful concerning FDA matters. Friendships provide access where it might otherwise not exist. And it provides an aura of trust and respect that probably would not exist in most adversarial situtations.

It can work this way:

William Vodra, formerly in the general counsel's office, is now with Arnold & Porter, a prestigious law firm representing several major pharmaceutical companies. To get swifter action on the approval of Pfizer Inc.'s new anti-arthritis drug, Feldene, all Vodra had to was pick up the phone.

A year ago he called J. Richard Crout, then director of the Bureau of Drugs, with whom he once worked. A memorandum of their telephone conversation written by Crout stated: "Mr. Vodra was trying to calm Pfizer but that the situation was getting worse and Pfizer was considering appeals to the bureau director and commissioner. He also said that pyroxicam (Feldene) is being used widely in the political arena and before the McMahon Commission as an alleged example of agency inefficiency."

Vodra defended the call, saying he did not attempt to influence the FDA decision. The drug was already approved. It was merely a question of getting the final letter of approval out.

The letter was sent out about four weeks later.

Vodra is the lawyer Hutt hired to rewrite regulations to allow new drugs to be marketed faster. But other priorities came along in the late 1970s and Vodra never completed his rewrite. He said many projects he worked on until 1979, when he left, are only now coming to fruition.

But delay is not the fault of lawyers, said Vodra. "It comes through a shifting of priorities, a demand for higher proof that what you're doing is correct and will absolutely be defensible in court, the zero defect mentality, the desire to do things comprehensively instead of in a piecemeal fashion. It has come from a desire to write in plain English instead of legalese."

The FDA chief counsel, Thomas Scarlett, was brought to the FDA by Hutt.

But Scarlett could not be interviewed for this article. By order of the secretary of the Department of Health and Human Services, the department's general counsel's office is no longer open to public scrutiny. It is closed to the press.

UNDER REAGAN, THE FDA SIDES WITH INDUSTRY—PART 4

"One of the basic principles of regulatory reform is trust in the integrity of the private sector . . ."—Chief counsel, U.S. Food and Drug Administration, 1982.

"This administration has confused regulatory reform with no regulation."—Drug industry lawyer, 1983.

(By Judy Grande)

WASHINGTON.—The U.S. Food and Drug Administration, waving the Reagan banner of deregulation, has been steadily dismantling public safety programs that have been years, even decades, in the making.

Whether sanctioning the use of drugs with known health risks or cutting down inspection staff, the Reagan-appointed FDA leaders have repeatedly sided with industry instead of consumers on a variety of heath issues.

These actions come while opinion polls show interest in health and medicine at all-time highs.

A few examples:

The FDA has cut in half enforcement actions, including seizures and recalls of adulterated foods and drugs. The inspection staff has been reduced by 24 percent, from 1,183 in 1978 to 903 in 1982.

The FDA has proposed streamlining the approval of new drugs to get them on the market faster. Opponents say this exposes patients and drug experiment volunteers to added health risks.

The FDA shut down its antibiotics laboratory, which tested batches of pills for quality and potency. The FDA is now leaving those judgments to the firms.

The FDA scuttled a program that would have required manufacturers of certain hazardous drugs to supply informational leaflets with prescriptions.

"The message is out. The Reagan administration is not enforcing the food and drug laws," said Dr. Sidney Wolfe, director of the Health Research Group, a consumer health organization founded by Ralph Nader.

The FDA has never been a model agency, but it is significantly worse under Reagan, said Wolfe. "There is an unprecedented number of instances of deferring to industry."

Since 1981, when President Reagan appointed former Sen. Richard Schweicker, secretary of Health and Human Services (HHS), the agency has backed away from hardline regulatory enforcement. It strongly stressed instead the need for voluntary compliance, which gives firms an opportunity to correct deficiencies on a voluntary basis.

An April 1983 report by the U.S. General Accounting Office (GAO) criticized this form of regulation, saying the FDA does not know to what extent voluntary compliance is working. In three of the four cities where GAO reviewed inspections, "no evidence was found in over half the cases to indicate that investigators had followed up on previously identified violations of the law and FDA regulations."

Commissioner Dr. Arthur Hull Hayes, Jr., appointed by Schweicker to head the FDA, disagrees strongly that formal enforcement actions are the only way to go.

"I think it is as fallacious to decide if we are upholding the Food, Drug and Cosmetic Act by the number of enforcement actions as it is to decide if it is safe to walk in Washington by the number of tickets given out," said Hayes.

"I think one should also go out in the streets and look. Are there people that are sick out there, that are not being served? Are there drugs out there that are helping people?

"It seems to me the test of whether the agency is doing its job is how well the public is being served. How well it is being protected."

Wolfe and others say not very well.

Among other examples, Wolfe points to the withdrawal of an HHS plan to put warning labels on aspirin bottles that use by children could cause Reye's syndrome, an ailment that strikes suddenly, causing vomiting and fever and, in some cases, death.

There is reason to doubt the reliability of the private sector, despite the belief of FDA counsel Thomas Scarlett that ". . . in most instances it can be relied on to safeguard the interest of consumers."

In 1980, the FDA examined 7,118 domestically manufactured drugs and found violations of quality or labeling in 1,153 of them. In 1982, 6,410 samples were examined and violations were found in 1,061.

Problems with imports are far greater, with as many as 70 percent of the drugs tested failing to meet U.S. standards.

Some violations have, in the FDA's judgment, warranted criminal investigation. In 1980, the FDA banned a Smith Kline Corp. anti-hypertension drug because 60 deaths were associated with its use. It was later discovered the company may have suppressed data on liver damage.

It is also investigating whether Eli Lilly & Co. withheld information on deaths associated with the use of Oraflex.

"This administration has confused regulatory reform with no regulation," said William Vodra, who worked in the FDA counsel's office in the late '70s. He now works for the law firm of Arnold & Porter, and represents many drug companies.

"The drop in enforcement is being perceived by the drug industry as ordered by Reagan. What can happen is they start taking bigger gambles. They, after all, might not get caught."

Though the FDA denies it has ordered a slowdown in enforcement activities, it is the perception that counts, said Vodra.

"The FDA is a mature agency. It can read election results as well as anybody else. Nobody has to tell them Ronald Reagan wants less regulation. If Ted Kennedy is elected in 1984, you don't have to send Telexes (teletyped reports) to the fields to start enforcing."

Another major concern of consumer groups, including the American Public Health Association, is the plan to streamline the drug approval process.

These recently proposed regulations would reduce reporting requirements on drug studies, accept foreign data as a sole basis of approval of a drug, tighten time frames for agency review of new drug applications and give much greater freedom to physicians who test drugs during the early phases of human research.

"Rather than the approval of new drugs, we believe the FDA resources should be directed toward removing ineffective prescription drugs from the market, and expediting the interminable over-the-counter drug review," the American Public Health Association wrote to Schweiker in February, just before he left government.

Schweiker, however, considered these regulations to be the most significant reform in the drug laws since the 1960s. They were among his last official efforts.

The pharmaceutical industry has sought such reform for years, but its spokesmen say the FDA has not gone far enough toward relieving industry of the financial and regulatory burden of developing new drugs.

The industry says it costs $70 million to develop a new drug and takes about three years for the FDA to approve it.

A November 1981 GAO report, however, estimated average approval time by FDA was down to about 11 months for important drugs (those offering breakthroughs in treatment) from 17 months in 1977.

In addition, drugs that offer significant therapeutic advances have been on a fast-track approval system for some time, negating the industry's position that important drugs are being kept off the market.

Accutane, Hoffman-LaRoche's advance in the treatment of acne, was approved so quickly earlier this year that the firm that was not ready to market it.

Of 27 new drugs submitted for approval in 1981, only two were classified by the FDA as providing important therapeutic gains and 11 as modest therapeutic gains. More than half the time was spent reviewing applications for drugs the FDA considered of little or no therapeutic gain.

The FDA has made drug approval a priority. It has reduced staff in other divisions, such as inspections, while keeping the drug evaluation division stable. In 1984, the FDA plans to reallocate 35 staff years and $1.2 million from "lower priority activities" to the new drug division.

The acceptance of foreign studies as proof of a drug's safety and efficacy is also a concern to health groups because the FDA has no authority to monitor studies in other countries. Timolol, a drug for high blood pressure, was approved recently on the basis of a Norwegian study.

Robert Temple, acting director of New Drug Evaluation for the FDA, agreed there are legitimate concerns about using foreign data, but added that the new regulation only says the FDA may accept it.

Hayes said the FDA is developing a drug approval policy that "assures safety and efficacy by today's standards but allows us to do that in a well-ordered way so that safe and effective drugs are developed, reviewed and approved and get on the market to patients where they are needed as quickly as possible."

Hayes also plans to define efficacy for the first time. Under the 1962 amendment to the Food, Drug and Cosmetic Act, drugs were required to be effective, as well as safe—but Congress did not define efficacy.

FDA critics fear Hayes is going to lower efficacy standards.

Reagan, during his campaign in 1980, backed repeal of the efficacy requirement, a step even drug companies opposed.

But Hayes said he is not attempting to reduce the standard, only provide a working definition for the FDA.

Some, however, say it is too late. Rep. L. H. Fountain, D-N.C., before he retired from Congress last year, cited the approval of Feldene as an example of lessening efficacy requirements.

Feldene is non-steroidal drug for arthritis, which the FDA said is no more effective than aspirin and may have additional side effects.

But Temple, who has the final say on all drug approvals, said, "The law is clear. You have to prove a drug is effective for its purpose. It does not say it has to be better. It can even be worse."

These are but a few of the changes brought about by the Reagan FDA, most of which were recommended by the drug industry. The changes are not cost-saving measures made by a financially strapped federal agency. Instead, they save money for one of the world's most profitable industries.

Shutting down the antibiotics testing lab is one example. Most of its cost was paid for by the drug manufacturers, not the FDA. The manufacturers expect to save several millions of dollars.

The pilot program to give out information leaflets to patients on drug side effects also saved the government nothing. It was eliminated, despite a 1982 survey by Chilton Research Inc. in which nearly 70 percent of consumers surveyed said they were not told about precautions and possible drug side effects by their doctors.

But drug industrialists and pharmacists strongly objected to the proposed patient package insert program, saying it would be too costly for the manufacturer, too time consuming for the pharmacist and too frightening for the patient.

The FDA commissioner bought that argument and said a citzens group should handle the task of better informing consumers. Thus, the National Council on Patient Information and Education was formed.

Its first major effort was to enclose a message on the proper use of prescription medicine with the July 1 checks to the nation's 36 million Social Security recipients.

Who paid for the printing and mailing?

The taxpayer.

FDA IS DWARF AGAINST GIANT DRUG INDUSTRY—PART 5

(By Judy Grande)

WASHINGTON.—The pharmaceutical industry spends $2 billion a year to promote its drugs. The U.S. Food and Drug Administration spends about $1 million to make sure the promotion is truthful.

Pharaceutical firms place 20,000 advertisements in medical journals each year. The FDA has time to scrutinize only 500 of them.

Pharmaceutical firms in 1981 spent $630 million on sales agents who hawk pills to physicians. That is nearly twice the size of the entire FDA budget.

The FDA, the only federal agency mandated to protect the public from unsafe drugs, is a regulatory dwarf amid pharmaceutical giants—outspent, out numbered, and often outmaneuvered by the industry it is supposed to control.

The division of drug advertising and labeling is particularly hard pressed, with its cadre of five scientists who try to review the advertising and promotional campaigns of more than 150 pharmaceutical firms.

The task become more difficult each year as companies find new ways to peddle their products—from lectures, slide shows and seminars to telephone conferences, video sessions and home computers.

Competition in the drug industry is fiercer every day as more and more products come on the marketplace. In 1981, consumers spent $14.2 billion on prescription drugs, an increase of 12 percent from the year before. Last year, 1.5 billion prescriptions were filled.

With the heightened competition comes an ever-increasing bending of the rules, said Lloyd G. Millstein, Ph D. acting director of the FDA's drug advertising and labeling division.

Making Millstein's task as industry watchdog more difficult is the FDA's after-the-fact role. It cannot pre-clear ads. It can only act if promotions are misleading or untruthful.

They sometimes are.

From October 1982 through February 1983, the FDA skimmed over 8,000 ads and 3,000 promotional pieces. Of those, 300 were monitored in depth.

The result: 170 regulatory actions, ranging from minor to serious violations, and 85 ads and promotional pieces canceled.

Some are resolved quickly by agreement with the firms, said Millstein, who worked for the drug industry for 20 years. Others take more time.

It took six months for the FDA to settle a dispute over Pfizer Inc.'s promotional campaign for an angina drug called Procardia.

The FDA called the promotions false and misleading, "based on untruths, partial truths and omitted information" and said it increased the risk of serious adverse reactions to patients.

The FDA concluded that side effects were understated, benefits were overstated, and it was advertised for a use for which the drug was not approved.

"This misleading campaign comes at the particularly crucial time of first introduction of nifedipine (the generic name of Procardia) to many American physicians who are not yet familiar with the important precautions they need to know in order to use the drug safely," the FDA wrote Pfizer.

The violations were discovered in April 1982. It was six months before Pfizer sent a letter to doctors stipulating the FDA's objections and correcting its promotion of Procardia. The FDA said it had no way of estimating how many patients were put at risk in the interim.

The FDA lacks authority in another important area—the distribution of press releases.

"We don't regulate press kits. It's against the First Amendment, unless it is used for promotion," said Millstein. "As long as it is not false and misleading there is nothing we can do." But more and more press releases to announce new drugs have the effect of promotion, as opposed to news.

When Eli Lilly & Co. introduced its new anti-inflammatory arthritis drug, Oraflex, last spring, more than 6,500 press kits were sent out touting the new drug and its possible revolutionary ability to regress arthritic disease.

It sold a half-million prescriptions in its first 12 weeks.

But there was not evidence that Oraflex would treat the disease.

The FDA sent out a so-called regulatory letter to stop the promotion. By that time, Oraflex had been pulled off the market because of more than 70 deaths associated with its use here and in Great Britain.

It takes months, often years, for the agency to take any regulatory action, unless there is an obvious imminent hazard.

With Oraflex, the deaths were not immediately known by the FDA. The regulatory letter was aimed only at the false claims about halting the disease.

But because of those claims, Millstein said, "it sells that many more prescriptions and that many more people die."

A similar promotion problem occurred with Feldene, also approved last year for relief of arthritic pain.

The FDA told Pfizer, Feldene's manufacturer, that its press kit was misleading, saying it falsely claimed Feldene was superior to aspirin, and that it may have a beneficial effect on the disease process.

"In light of the complaints made by your company concerning the press Release and subsequent publicity concerning a competing product (Oraflex), we find the information contained in your press release surprising," the FDA wrote to Pfizer.

The FDA tries to monitor numerous other areas, including teleconference and video sessions, where groups of physicians sit down together to discuss a particular product used in their medical specialty.

This poses another problem for an already overworked division: how to keep track of every call made or tape sent by industry to doctors.

One problem with the Pfizer promotion of Procardia dealt with a videotape featuring five prominent cardiologists discussing uses of the drug.

Despite the severity of the disease for which the drug is intended, the videotape contained no precautionary information, such as the drug's ability to cause "profound hypertension," the FDA wrote to Pfizer.

In addition, a Harvard Medical School cardiologist suggested Procardia was useful for heart attack patients, a claim not approved by the FDA.

The Pharmaceutical Manufacturers' Association (PMA), which represents 145 firms, says the purpose of advertisements and other promotional efforts is to provide physicians with information after the need for a product has been determined, not to promote use when no need exists.

The PMA has a code of marketing practices pledging members to "provide full scientific information with scrupulous regard for truth in all matters."

The PMA says it has reason to comply with the FDA's regulations because its products are subject to seizure if they disobey the law.

FDA records show, however, that at least a third of the nearly 500 seizure actions approved from 1979-1981 resulted in no products seized.

This stems from the FDA's inability to detain drugs produced in the United States. A recent report by the U.S. General Accounting Office said that by the time the FDA got approval from its counsel's office to seize the products, drugs found to be in violation were already shipped to the public.

Amid these difficulties, there is perhaps a larger problem looming.

Many pharmaceutical firms are taking their campaigns directly to the consumer—through television and magazines.

Realizing the potential for trouble, FDA Commissioner Dr. Arthur Hull Hayes, Jr. has asked for a moratorium until the FDA has a chance to study the issue.

The FDA will test consumer reaction in four cities—Cleveland, Buffalo, New Orleans and Seattle. Volunteers will view simulated TV ads for prescription drugs or read magazine ads, and then fill out questionnaires.

At a recent public meeting of health professionals, Ciba-Geigy Inc. presented to Hayes a mock TV ad for Constant T, a drug for bronchial asthma. "It can help you forget about breathing, so you can start living" said the voice on the TV set.

This informal approach is familiar to consumers of over-the-counter drug products that come under the jurisdiction of the Federal Trade Commission. But prescription drugs carry more serious side effects.

"When Congress wrote the law (in 1962) it assumed advertisements would only be directed to the doctors. They never thought otherwise," said Millstein. "Now Congress is in a position to answer industry's question: 'Why can't we?' "

Hayes said fundamental questions have to be answered before a decision is made, "What is the advertising for? Who will it serve? What is its purpose? Who will it help? And who will it hurt?"

The FDA approved, on a trial basis, direct advertising on Cable Health Network, a nationwide cable TV service. It began last month.

Joe Boyd, Ciba-Geigy's director of public relations, said the industry's interest in direct advertising to consumers stems from the public's desire to take a more aggressive role in health care.

Advertising in the mass media, instead of in medical journals alone, should benefit consumers by making them aware of different therapies available, said Boyd.

It would also make them aware of products that benefit the companies materially.

Ciba-Geigy, however, has made no firm decision yet on direct-to-consumer advertising.

There has been a breach of the voluntary moratorium by a British-owned company, Boots Pharmaceuticals Inc., which is advertising its arthritis drug, Rufen, in Florida.

Boots is running a TV commercial stating that Rufen is cheaper than Upjohn's Motrin, the identical drug. Boots has also taken out ads for Rufen in several Tampa area newspapers.

Upjohn has filed a complaint against Boots, which the FDA is reviewing.

"They are flouting the moratorium in our face," said Millstein.

But consumer advertising seems to pay off. Last year, Boots advertised a $1.50 rebate with Rufen prescriptions and received 19,000 rebate coupons within 14 months. It has captured 8 percent of the market for that type of drug.

Health professionals are worried, however. Some say it will lead to overuse and addiction. Many say consumers will not be able to understand the risks associated with the drugs.

The American Association for Retired Persons and several consumer health groups are flatly opposed to direct advertising.

Even some companies are concerned. A representative of Merck, Sharp and Dohme said its concern is that some health decisions can only be made by qualified professionals. If the concept is approved, the Merck spokesman said, companies should voluntarily preclear ads with the FDA.

Doctors have not responded favorably to the idea yet, either. Surveys have shown that 70 percent oppose consumer advertising because it may put undue pressure on them to prescribe a certain heavily advertised drug. But the American Medical Association has not yet taken an official position, saying it is still studying the issue.

Former Sen. Gaylord Nelson, who held many hearings on the pharmaceutical industry in the 1970s, is not wavering. "There would be tremendous pressure on physicians if direct advertising to consumers is permitted. And what is the purpose of it? The only conceivable purpose is to expand the unncessary use of prescription drugs. It's an open invitation to the drug industry to really corrupt the public.

"If the American medical profession is worth a damn it ought to be up in arms about this. If the FDA and the AMA don't come out strongly against this, they're selling out to special interests. That's all there is to it."

Drug Industry Wields Powerful Political Clout—Part 6

(By Judy Grande)

Washington.—Former Sen. Gaylord Nelson of Wisconsin tried for eight years to sever the ties between the drug industry and the doctors hired to test drugs before they get on the market.

Nelson, a popular, respected Senate Democrat, could not persuade his fellow senators to break up what he said was an unwholesome relationship between drug makers and drug testers. His bill never even got a hearing.

Nelson got plenty for his troubles, though. Drug firms contributed $4,750 to the campaign of Rep. Robert Kasten, who defeated Nelson in 1980. Nelson got no drug company money. This year, Kasten proposed a product liability bill that has the drug industry's enthusiastic endorsement.

The pattern is familiar. Recently, Congress has done little to protect the public from unsafe drugs, but quite a lot to protect the pharmaceutical industry.

Despite repeated attempts, no major drug reform bill has been passed since 1962, when the late Sen. Estes Kefauver of Tennessee successfully fought for amendments requiring drugs to be effective as well as safe. Since that time, Congress has repeatedly failed to reform the nation's drug laws and give the U.S. Food and Drug Administration (FDA) greater power to enforce those laws.

Among the failed attempts:

Congress did not pass a 1976 bill that would have placed restrictions on promotions by drug sales agents and a ban on gifts and samples to physicians.

Congress rejected in 1979 legislation requiring drug firms to conduct post-marketing and scientific investigations of approved drugs and would increase the FDA's authority to impose civil penalties. The same bill would have given the FDA subpoena power and authority to order drug firms not to distribute questionable drugs. Bills seeking this detention authority were submitted in each Congress from 1974 to 1980.

Congress never even considered a 1980 bill that would have required the dissemination of infomation on the risks of drugs on pregnant women.

Congress has, however, several times in recent years granted tax credits and incentives to an industry that is already one of the most profitable, and last year failed by only five votes to extend by as much as seven years the 17-year patent rights on drugs.

Pharmaceutical company supporters have also attempted, though unsuccessfully so far, to repeal Kefauver's drug efficacy requirements.

This year, even before the 98th Congress was in full gear, drug company lobbyists were back swarming on Capitol Hill, trying to find new sponsors for the patent bill and others that would add to the firms' already impressive bottom line. And as in years past, members of the House and Senate responded quickly to the call of the companies that contributed more than $750,000 to the 1982 congressional campaigns.

Sen. Charles McC. Mathias Jr., R-Md., has reintroduced the patent bill and has held the first of two hearings before a Senate Judiciary subcommittee.

The Mathias bill, which breezed through the Senate by voice vote in 1981, would allow seven years of additional patent protection for manufacturers whose drugs are subject to federal regulatory review. Companies contend that the FDA takes so long to approve new drugs that patent life is nearly gone before a drug gets on the market. This stifles innovation and leads to decline in research, they say.

And, like the 1981 bill, it applies to all manufacturers undergoing pre-market approval of drugs. The House version, sponsored last year by the liberal Rep. Robert

Kastenmeier, D-Wisc., was not retroactive. It applied only to those drugs for which patents were obtained after enactment of the bill.

"Lobbying on this bill (Kastenmeier's) was one of the most intense I've seen in Congress. It seemed everybody had a personal friend working for one of the companies," said one House member involved in its narrow defeat, who asked not to be named.

"The drug companies are quite powerful. It's really that simple. Aside from contributions, they can arrange lots of speaking engagements. They have 10 or so executives sitting in a room. You say a few words and you get $1,000."

But the Kastenmeier bill, which, because it was brought up under a suspension of the rules needed a two-thirds majority of the House to pass, fell short by five votes. This year, he stayed away from the bill.

His former subcommittee counsel, Bruce Lehman, said Kastenmeier was disgusted. Tremendous personal pressure was put on him by the opposition, which included the generic drug industry, consumer groups and a few of his liberal colleagues, said Lehman. "He was burned out. He wanted to spend more time on important things."

After a brief search, the drug makers found Rep. Michael L. Synar, D-Okla., a member of Kastenmeier's subcommittee, who would carry their flag. He is drafting a bill said to be almost identical to the Senate version, including the industry-supported retroactivity.

Besides Nelson, there are a few other congressmen who, over the years, have taken on the pharmaceutical industry—Sen. Edward M. Kennedy, D-Mass., Rep. Albert Gore, D-Tenn., Rep. L. H. Fountain, D-N.C., and at times, Rep. John Dingell, D-Mich., and Sen. Howard M. Metzenbaum, D-O.

At the Mathias patent hearing last month, Metzenbaum argued that government regulations to insure drug safety and effectiveness do not unfairly eat away at patent life and decrease incentives to create new drugs.

"The pharmaceutical makers claim fewer and fewer drugs are being approved. As we will see, this is hogwash," Metzenbaum said. "The rate of drug approvals has gone up, not down, in recent years.

"The drug companies themselves predict that their market will triple in 10 years to a total of $217 billion in annual sales worldwide. Is there not a fantastic spur to innovate in itself?"

But behind the patent bill, which opponents argue will cost consumers more by keeping cheaper generic imitations off the market, is the Pharmaceutical Manufacturers Association, which last year spent about $200,000 for Capitol Hill lobbying. The PMA has also hired big names to tout its cause, with the leader being Peter Barton Hutt, a respected former general counsel of the FDA, who represents many major drug companies.

The industry has also tied itself to big-name Democrats, including the influential law firm Manatt, Phelps, Rothenberg & Tunney—Manatt being Charles Manatt, national chairman of the Democratic party. The firm was hired to lobby on behalf of the drug industry.

Central to the debate is the issue of drug lag—how long it takes the FDA to approve new drugs for marketing.

Congess became deeply involved in that issue as well last year, forming the Commission on the Federal Drug Approval Process.

But the commission report, a consensus document of volunteers from industry, academia and a few consumers, was little more than an industry wish list. It contained most of the recommendations industry has made over the years to streamline the drug approval process.

The commission was funded by Project Hope, a charitable organization active in health care overseas and in health issues domestically. Its board chairman is W. H. Conzen, former chairman of Schering-Plough Corp., a New Jersey-based pharmaceutical manufacturer.

The pharmaceutical web becomes more tangled when considering who lined up Project Hope to fund the commission—Jonah Shacknai, former aide to Rep. James Scheuer of New York, who set up the commission with Gore.

Shacknai has since left government to open his own law firm and now represents several major pharmaceutical firms.

Gore, a leading opponent of patent extension, challenged some of the commission's work but did not interfere with the report, said Thomas Grumbly, Gore's former staff director.

Grumbly, who was executive assistant to former FDA Commissioner Donald Kennedy, said the public did not pay for the study, except printing costs, so it was not appropriate for Gore to dominate the commission.

Congress has not been lax in one area—holding hearings.

Dozens of hearings have questioned why particularly dangerous drugs have been approved by the FDA and why the government's safety system fails. But few result in significant legislative changes.

Fountain, who retired last year, pursued the hearing format and was responsible for some administrative changes at the FDA. His successor as chairman of a government operations subcommittee, is Rep. Ted Weiss, D-N.Y. He appears to be following Fountain's footsteps, having held a hearing on the painkiller Zomax, recently withdrawn from the market because of fatal allergic reactions.

Rep. Mary Rose Oakar, D-O, of Cleveland recently held a hearing on drugs and the elderly that was highly critical of the FDA's system of drug protection.

Oakar said she was pressured by colleagues, as well as the pharmaceutical industry, to drop her hearings.

Ms. **Oakar**. Thank you, Mr. Chairman.

Mr. **Pepper**. Thank you very much, Ms. Oakar.

My Florida colleague now, Mr. Bilirakis.

STATEMENT OF REPRESENTATIVE MICHAEL BILIRAKIS

Mr. **Bilirakis**. Thank you, Mr. Chairman.

I too, sir, would like to congratulate you for calling this most important hearing, and to commend Ms. Oakar for suggesting it. I would also like to commend the Thompson Medical Co. representatives for appearing and being willing to serve. I personally was disappointed when we recently joined with the Senate to hold the hearing on the misuse of drugs, and the pharmacy companies were not represented. I thought that was pretty terrible, and I was very disappointed.

So, I commend Thompson for appearing.

This subject matter is a serious concern to me, as I represent the fastest-growing area in the Nation when it comes to senior citizens. I should add their primary concern is health care, of course.

I feel that this hearing will provide us with much needed information at a time when many Americans are concerned about drugs that they can purchase over the counter, not only for the efficacy of the product, but also its safety.

Though this hearing is certainly geared in another direction, we, Mr. Chairman, must not forget the recent tragic events that have taken place with—I sometimes think—too easily available over-the-counter drugs.

Health-related professionals, including doctors, nurses, and pharmacists—and we prepared for this hearing by going to the grassroots, by contacting personally medical doctors and pharmacists and others in our area to help us get together some of the problems—have all expressed their concerns with over-the-counter drugs. They expressed concern that a great misuse does take place as many of our citizens do not bother, as Mr. Regula mentioned, to read the instructions. They often misunderstand them and still others cannot read or comprehend the instructions.

I feel that I should also mention the growing concerns of many professionals over nonprescription drugs being sold in grocery stores, self-service operations, and even hardware stores. These drugs are purchased there to save a little bit of money, since the price of prescription drugs is often too expensive for a limited budget and many times is not tax deductible.

The alternative is over-the-counter drugs which are not always as effective and often do not work with the efficacy that prescribed medicine usually does.

Mr. Chairman, I'd like to bring to your attention and to the attention of the listening audience a survey which was recently conducted in my district by Operation P.A.R. [parental awareness and responsibility], a group which ordinarily deals with the misuse of drugs by youth. But this survey clearly indicated more than 50 percent of the elderly persons, those 60 and older, who were surveyed, were taking medicine in a dangerous manner. According to the survey, 49 percent of the survey participants use over-the-counter drugs; 44.5 percent of them use them with prescribed medications.

Seventy-one percent never or only sometimes consulted their physicians when using over-the-counter drugs.

Mr. Chairman, I could continue but time certainly does not allow it. Thus, I ask your unanimous consent that the entire survey be submitted for the record, and I commend its results to the committee.

Thank you, Mr. Chairman.

Mr. PEPPER. Without objection, it will be received.

[See app. 1, p. 223 for material submitted by Representative Bilirakis.]

Mr. PEPPER. Mr. Lantos.

STATEMENT OF REPRESENTATIVE TOM LANTOS

Mr. LANTOS. Thank you very much, Mr. Chairman.

First, Mr. Chairman, it's an enormous pleasure for me to commend you for your unceasing efforts on behalf of our Nation's elderly. May I just say, parenthetically and privately, that I saw you at 10 o'clock last night on the floor of the House when we concluded the MX debate. I understand you were up at 5:30 this morning to appear on a network television program. If you will just tell us what OTC medication you are using, I think we'll all be way ahead.

Before I make a couple of comments of a substantive nature, I want to apologize, Mr. Chairman, that I am to give a brief testimony on the Senate side and will be back right after that.

These are enormously important hearings, and I view my responsibility as a professional economist of putting them in some kind of perspective. They are analogous to hearings relating to highway safety or airline safety, because they deal with human tragedy. Tomorrow another subcommittee of the House will hold hearings on airline safety in San Francisco, and we will be focusing on the tragedies that occurred during the last few years with respect to airline safety.

Yet, at the same time we'll be focusing on the fact that the overwhelming bulk of Americans who use air transportation have open to them a whole new arena of public service by safely and comfortably and relatively inexpensively using a means of transportation that, in a different generation, was just dreamed of.

I think we have a similar problem with highway safety. Fifty thousand individuals are killed on our highways each year, Mr. Chairman, and I think every one of those represents an enormous human tragedy. Yet, we are not talking about terminating the use of the automobile. What we talk about is developing safe highways, safer automobiles, better-trained drivers.

And I believe it's critical that in dealing with over-the-counter medicines we differentiate between the use by millions of Americans of safe and effective over-the-counter medications and the fly-by-night companies which put on the market with irresponsible advertising dangerous products and the problems that are created by user misuse, abuse, ignorance.

I was intrigued at our last hearing, Mr. Chairman, that many of the problems we discovered in dealing with prescription medications are, of course, applicable to over-the-counter medications, and they are generic in character. For instance, taking 5 times, 10 times, 100 times the prescribed dose. It has yet to be explained to me how there is a difference between a consumer taking an overdose of a prescription medicine and the consumer taking an overdose of a nonprescription medicine.

If the problem is more effectively designating on the label the proper dosage, this is a generic problem which I think is equally applicable to both.

I was very much impressed, Mr. Chairman, by the problems that stem from mixing of medications. But you can mix prescription medicines with prescription medicines, over-the-counter medicines with other over-the-counter medicines. You can cross-mix. And I think the problem, again, is generic.

I will be very much interested in what we economists call, a cost-benefit analysis. If, in fact, there are *x* number of individuals who, in fact, suffered by taking medications or abusing medications, whether it's prescription or over-the-counter drugs, I'd like to put that in the statistical framework of the tens of millions who benefit from this.

In your opening remarks, Mr. Chairman, you talked about Contac. Don't take away my Contac. I use it several times every year when I have a cold and I would deeply resent having to go to a physician to obtain Contac, which today I get at the drug counter at Safeway and I suspect along with millions of other Americans, it gets rid of my cold very fast.

Our grandchildren are using cough medicines. I looked at the labels of those cough medicines and those cough medicines contain PPA. I would hate to see that cough medicine taken away from my grandchildren just because there may be anecdotal experience of adverse reaction to PPA by some. But I'm really suggesting, Mr. Chairman, that we have got to conduct our investigation, as I know you intend to, in a broad framework, recognizing that if, in fact, tens of millions of Americans like myself take over-the-counter medications, from cold medicines to diet medications to cough medicines, we must give some credit to their intelligence. We must give some credit to the intelligence of the parents and grandparents who allow children to take cough medicines, because there clearly are no adverse side effects. If there were we would stop doing this. And because the benefits are self-evident.

Finally, Mr. Chairman, I think we have got to give the FDA at least the degree of fairness in our approach to them. These are honest public servants who are likely to be making far more money in the private sector, who have chosen to dedicate their professional expertise to protecting the public health, and to suggest that there is some strange conspiracy between the FDA and other elements in society allowing the FDA to go ahead with the use of unsafe drugs raises some serious questions in my mind.

I thank the Chair.

Mr. PEPPER. Well, thank you for your very informative statement, Mr. Lantos.

Next, Mr. Daub.

STATEMENT OF REPRESENTATIVE HAL DAUB

Mr. DAUB. Thank you very much, Mr. Chairman. I will be brief. I'm going to first attempt, because I have such great respect for our chairman and for the leadership of my ranking member, Mr. Regula, and because I appreciate the innovative, as always, and constructive, efforts that my good friend, Mary Rose Oakar, makes, particularly since we give her credit for this hearing, to pronounce the word that you've all been hearing a description of, called PPA. I had trouble with it and I tried. So, I thought before we get started with our panel, who has been so patient, that I would attempt to pronounce that word: phenylpropanolamine. Did I come close to pronouncing it correctly?

But now you may know, if you don't, in the audience what we were talking about, and indeed, I hope I came close. But PPA.

I too, Mr. Chairman, am very concerned about insuring the safety and efficacy of over-the-counter drugs such as PPA. However, with all due respect, I question some of the methods that can be used to focus on this issue. Bringing up extreme cases regarding adverse reactions from the use of, for example, PPA, in front of TV cameras and other media, can be misleading and create misleading impressions when dealing with this area of concern. It is our duty to highlight possible dangers, particularly with this committee's jurisdiction, in order to protect our senior citizens. But we must take care not to resort to scare tactics to accomplish this and, indeed, if we're not careful, we could engage in counter-productive results.

Such scare tactics would encourage those who are using drugs safely and efficiently and effectively for more important purposes to abandon that safe and appropriate use. This type of matter concerning the safety and efficacy of drugs should be dealt with in a scientific arena during an oversight hearing with experts testifying. And I'm glad to see that some of these experts will be included in the hearing.

Virtually anything taken in excess will have negative effects. PPA, too, when used in ways other than those authorized and/or written in terms of label instructions, could, indeed, be dangerous. Appropriate labeling requirements are important for over-the-counter drugs, and I'm glad to see that this subcommittee will have the opportunity to review current labeling on the OTC drugs.

In addition, it is important to insure that the Food and Drug Administration is not lax with respect to its duty of insuring that the safety and efficacy of drugs be maintained for our citizenry at large.

Regarding PPA, the FDA approved this drug as safe and effective after 4 years of reviewing the literature and the data on the drug. They approved it pending further study, and I think the record should show that, and they have since that time asked for new research on aspects of the drug that are being questioned. This is an important issue for our elderly population. As you've already heard, of the noninstitutionalized elderly, 70 percent use over-the-counter drugs compared to only 10 percent of our general population.

It is my hope that this hearing will highlight the importance of appropriate labeling requirements and work with the Food and Drug Administration authorities in approving the over-the-counter drug, I think, proliferation that indeed, simply because of cost and great scientific research, will be an even greater part of our marketplace in the future.

And, indeed, with our help we hope that this combined effort will be with consumer advocates a very responsible approach.

I want to thank all of the witnesses who will be testifying today. We have, indeed, an impressive list of witnesses. And I look forward to hearing their testimony and, again, want to particularly thank, Mr. Chairman, Ms. Oakar for her leadership in this matter.

Mr. PEPPER. Thank you very much, Mr. Daub.

Now we have a very outstanding panel of over-the-counter consumers and consumer representatives. I will call their names and then they will come forward. For overview, Dr. Sidney Wolfe, director, Health Research Group, president, Public Citizen, a nonprofit citizens' organization founded by Ralph Nader. Mrs. Anthea Sacks of Westport, Conn., Ms. Gloria Jean Davis of Albany, Ga., Mrs. Janey Phipps, resident nurse, of Gray, Ky., and Mrs. Kathleen O'Reilley, consumer expert, National Broadcasting Co.

First we'll call on Dr. Sidney Wolfe.

PANEL 1—OVER-THE-COUNTER CONSUMERS AND CONSUMER REPRESENTATIVES, CONSISTING OF SIDNEY WOLFE, M.D., DIRECTOR, HEALTH RESEARCH GROUP, AND PRESIDENT, PUBLIC CITIZEN; ANTHEA SACHS, WESTPORT, CONN.; GLORIA JEAN DAVIS, ALBANY, GA.; JANEY PHIPPS, R.N., GRAY, KY.; KATHLEEN O'REILLEY, CONSUMER EXPERT, NATIONAL BROADCASTING CO.; AND FRANK ADAMO, JOHNSON CREEK, WIS.

STATEMENT OF SIDNEY WOLFE, M.D.

Dr. WOLFE. Chairman Pepper and members of the subcommittee, thank you for the opportunity of testifying before this all-too-rare congressional hearing.

As you mentioned before, there are a large number of hearings on prescription drugs and nowhere near as many as there should be on over-the-counter drugs. I'm glad to see that you're starting, hopefully, a good precedent.

Americans will spend approximately $8 to $10 billion, depending on which set of figures you look at, this year on over-the-counter drugs, but in many ways over-the-counter drugs they buy are not much of an improvement over those available around the turn of the century. A few advances, such as dextro methorphan, for coughs, are overshadowed by the fact that various products which would then have been called snake oils still dominate the over-the-counter drug scene.

According to William Gilbertson, Chief of the Food and Drug Administration's OTC Drug Review, by 1981 only one-third of the OTC drug ingredients reviewed by expert panels called in by the FDA, have been shown to be safe and effective for the intended uses. A more recent analysis of the now 1,819 OTC ingredients which have now been reviewed shows that only 422 or 23.2 percent, have been found safe and effective for the intended uses.

Of the 466 top-selling over-the-counter drug products, almost one-third of them contain ingredients which FDA expert panels have found lack evidence of safety, effectiveness, or both. More than another third, an additional third, contain ingredients which, like phenylpropanolamine [PPA] lack evidence of safety, effectiveness, or both, according to physicians at Public Citizen, a health research group, and many consultant physicians around the country.

Thus, over two-thirds of the top-selling 466 over-the-counter drug products in this country contain ingredients which lack evidence of safety, effectiveness, or both. This information is in a book which will be published this fall by Pantheon titled "Over-the-Counter Pills That Don't Work."

The following 9 examples of top-selling OTC drugs, all in the top 40 drugs in 1981, with annual sales of over $524 million, all contain 1 or more ingredients lacking evidence of safety, effectiveness, or both: Anacin, Listerine, NyQuil, Preparation H, Excedrin, Dristan tablets, Scope mouthwash, Robitussin cough syrup, and SinuTab. Preparation H is an interesting one when one thinks about snake oil, because one of the ingredients in it, the active ingredients, is called shark liver oil. Another one is called live yeast cell derivative. Neither of these ingredients, as they exist in Preparation H, were found to have evidence of effectiveness by the FDA Advisory Panel.

As a result of this, Americans are wasting at least $3 or $4 billion a year on over-the-counter products which contain ingredients lacking evidence of safety or effectiveness, or which are overpriced. In addition, millions of people are being exposed to unnecessary health hazards of ingredients such as PPA, which is too dangerous for OTC use in diet pills, and hundreds of other ingredients which, in the absence of evidence of effectiveness, provide risks without benefits.

Why, given strong laws such as the Federal Food and Drug laws and the Federal Trade Acts, does this wasteful and dangerous state of affairs exist? There are two important forces to protect consumers from dangerous or ineffective drugs, in one instance and from being defrauded in the marketplace in the other instance.

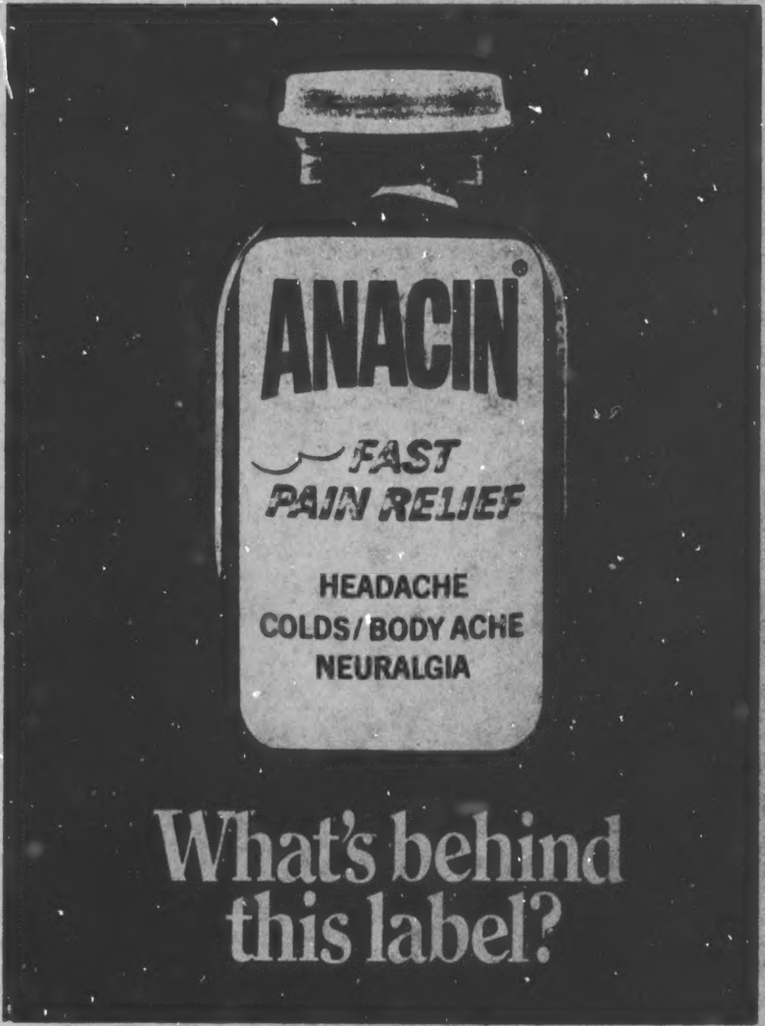
The first is Government regulation by the Food and Drug Administration over the safety and effectiveness of drug ingredients. The second is FTC action to allow marketplace forces to operate properly by insuring that the power of information, as in advertising, is not converted into an abuse of power by false and misleading promotional campaigns. Both the FDA and the FTC responding to pressure from the drug industry, are doing a decidedly inadequate job of upholding their respective laws.

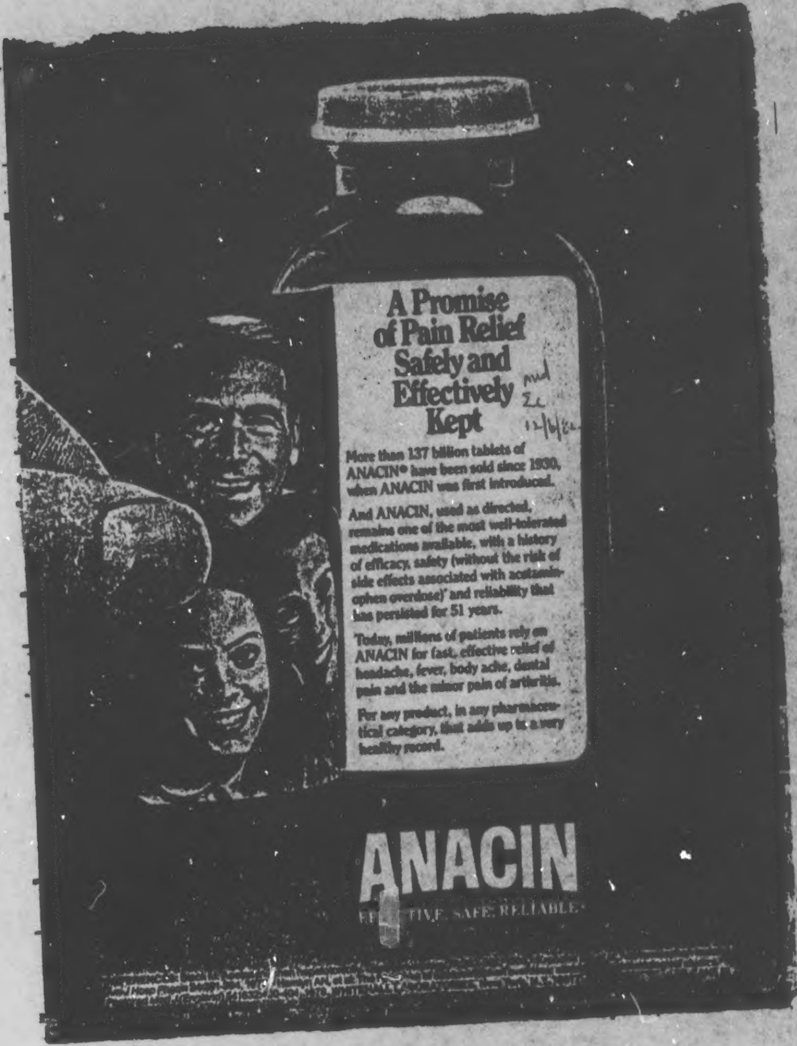
While FDA's over-the-counter drug review can only be described as a major disaster from the consumer viewpoint, it is well thought of by the OTC drug companies whose trade association, the Proprietary Association, is an intervener on the side of the defendant, the Food and Drug Administration, in a lawsuit we have brought, pending in the U.S. court of appeals, which challenges the legality of this drawn out O.T.C. drug review which has failed to take these ingredients, lacking evidence of safety or effectiveness, off the market.

The FTC, in the last 2 years, has done even less policing of OTC drug ads than previously. The recent FTC decision a couple weeks ago concerning OTC painkillers must have been pleasing to many OTC drug companies who saw that it was unaccompanied by any demand for corrective advertising and saw it as a retrenchment on the scope or breadth of cases in which ad substantiation would be required.

Despite an older FTC decision upheld by the U.S. Court of Appeals, Third Circuit, December of last year, which found that Anacin's manufacturer had engaged in large scale deception, in ads for Anacin and Arthritis Pain Formula, the misleading ads seen in the next two pages for Anacin appeared the same month.

[The material referred to follows:]


ANACIN
FAST
PAIN RELIEF
HEADACHE
COLDS/ BODY ACHE
NEURALGIA
What's behind
this label?



A Promise of Pain Relief Safely and Effectively Kept

mrd
Zc
12/6/82

More than 137 billion tablets of ANACIN® have been sold since 1930, when ANACIN was first introduced.

And ANACIN, used as directed, remains one of the most well-tolerated medications available, with a history of efficacy, safety (without the risk of side effects associated with acetaminophen overdose)* and reliability that has persisted for 51 years.

Today, millions of patients rely on ANACIN for fast, effective relief of headache, fever, body ache, dental pain and the minor pain of arthritis.

For any product, in any pharmaceutical category, that adds up to a very healthy record.

ANACIN

EFFECTIVE. SAFE. RELIABLE.

Dr. WOLFE. The reason I put this in is that it's an ad not over television or in a magazine, but in a medical journal, and the ad nowhere mentions that what's behind the label is aspirin. It mentions that acetominiphin, another painkiller, can cause toxicity and so forth, which is certainly true, but it is no more and no less true than for aspirin. But it fails to tell even doctors, many of whom I suspect are equally unaware as consumers, that the only ingredient in Anacin that is safe and effective for relieving pain is aspirin. The other ingredient, caffeine, lacks evidence of effectiveness.

Annual retail sales for the top five product lines of over-the-counter painkillers, the Tylenols, Anacins, Bayers, Bufferins, and Excedrins, were about $800 million in 1981, with advertising expenditures amounting to $150 million. Since the only safe and effective painkiller in these or any other over-the-counter drug product is aspirin or acetominiphin, consumers who buy these five product lines would save at least $400 million a year if they bought generic or house brand aspirin or acetominiphin instead of Anacin, Bayer, Tylenol, Bufferin, or Excedrin.

Rather than wasting money on overpriced brand names, some of which also have ingredients lacking evidence of effectiveness—Anacin and Excedrin—more and more people are responding to real competition on the basis of price, not contrived and deceptive differences in quality, and are buying generic or house brand painkillers.

Although the other witnesses, including both medical experts and victims, will discuss in more detail problems which appear to be associated with the use of phenylpropanolamine or PPA, I will briefly review its hazards. The following is taken from our book, "Over-the-Counter Pills That Don't Work."

"PPA is now the leading over-the-counter diet aid, accounting for almost $220 million in OTC pill sales." This is in 1981.

> With products such as Control, Dexatrim, Dietac, Permatheme, Prolamine, Thinspans, all containing the drug. No well-controlled study has shown that PPA is effective as an aid in long-term weight control. It may help you lose weight for a few days but you gain the pounds back when you stop taking it and it won't help you make the changes in diet and exercise patterns which are needed to keep weight off.

The FDA acknowledges that PPA is a hazard to a significant portion of the population, at least 20 percent. People who must avoid PPA include those with any of the following conditions: Hypertension or high blood pressure, heart disease, diabetes, or thyroid disease. The issue is made more serious by the fact that overweight individuals and hence people even more likely to use PPA, are more likely to suffer from all of these disorders discussed earlier. And here is a point which goes beyond any reading of the label. If everyone read the label we would still have a serious problem with PPA.

I agree fully with you, Mr. Chairman, when you say that a lot of people, perhaps particularly older people, don't read labels or can't keep 15 or more labels straight if they're using an average of 13 prescription drugs and another 5 or 10 over-the-counter ones. But even if they did, a lot of them would be in trouble. Because it's estimated that as many as 40 percent of diabetics and as many as 30 percent of all people with high blood pressure don't know that they have the disease. Therefore, even if they read the label, they would not believe that they are in the group of people who should avoid the drug.

The fact that they are overweight puts them at even a higher risk for diseases such as high blood pressure.

As mentioned before, negative reactions occur with the use of these drugs, even in recommended doses, although some of the adverse reactions have been seen with elevated doses. A study on normal medical students in Australia showed that there was an increased amount of high blood pressure in students after one dose of PPA. This study, unlike most of the ones you'll hear about at the end of today, was not funded by a drug company and I think it can therefore be more readily believed.

Because even if everyone read the label, many people would not know that they shouldn't take the drug, millions of people are unaware that they have a disease which may seriously be impaired by taking PPA, namely, high blood pressure or diabetes.

PPA is too dangerous and has an effectiveness which is too marginal or too short-lasting to be allowed for sale over the counter. Someday we will look back on the PPA decade, 1975 through 1985, and wonder who in the FDA was reckless enough to allow its use, or who in the FTC was reckless enough to allow its misleading ads such as one which ran for Maximum Strength Dietac, pushing, "A new diet aid without caffeine or other stimulants." Obviously, something that is in the same family as amphetamines and which has been shown in a number of cases to cause an increase in blood pressure and a number of other kinds of excitement of the central nervous system, is, in fact, a stimulant.

The clearest statement about the faddish business of diet pills comes from a drug company executive who said that in the sixties there were rainbow pills or thyroid stimulators. Then there were amphetamines followed by candy, CMC—or carboxymethylcellulose—benzocaine, and now PPA, which cannot last, either. You don't need any of them. If you have the willpower to cut down on your eating and to exercise, you lose weight. The drug company executive, of course, fails to mention that during these fads, there are many, many victims such as the people you will hear from in a couple of minutes.

I'd just like to close by saying, as has been said by people both to the right of you and to the left of you, that this is not meant to be an open-and-shut attack on over-the-counter drugs. In our book and in statements we have made over the 12 years we've been around, there are some very useful over-the-counter drug products. They are mainly single-ingredient products such as the painkillers, the acetaminophen and aspirin, the drug for treating coughs effectively, if you really need a cough suppressant, if you can't sleep at night and you aren't bringing up anything, dextromethorphan, and so on.

But most of the 300,000 over-the-counter drugs on the market are either overpriced or contain ingredients lacking evidence of safety and effectiveness and, as I mentioned before, are causing Americans to waste $3 billion or $4 billion a year.

The idea of self-treatment is a very important one, particularly in older people who are loaded up with too many drugs, both over-the-counter and prescription. Self-treatment is different from self-medication because many kinds of self-treatment don't necessarily involve medication. It's been said by experts from the National Institutes of Aging that elderly people really shouldn't be taking over-the-counter laxatives, one of the categories of drugs that they most frequently take.

Instead, they could use dietary means such as having larger amounts of liquids and higher fiber in their diet. This is just one example where self-treatment doesn't involve self-medication. But sometimes it has to involve self-medication. There are some safe and effective over-the-counter drugs around. If Americans focused on them instead of the much larger number that have ingredients that aren't effective, we would all be better off.

Thank you very much. I'd be glad to try and answer any questions you have.

Mr. **Pepper**. Well, thank you very much, Dr. Wolfe, for your excellent statement.

Our next witness is Mrs. Anthea Sachs of Westport, Conn. We are pleased to hear from you, Ms. Sachs.

STATEMENT OF ANTHEA SACHS

Ms. **Sachs**. In August 1980, I was anxious to lose 10 pounds before my son's wedding, and seeing a large display of diet pills by the checkout counter at the drug store, I asked the manager if they worked; it seems too good to be true. He said, "A lot of my customers seem to get good results with Dexatrim." After reading the warnings on the back and seeing I had none of the illnesses, such as high blood pressure, diabetes, or glaucoma, or any of the others listed, I thought it would be safe and bought the extra strengh size. I was on no other medication and, at 61, was in excellent health.

I took one pill a day, as directed, for nearly 3 months, went on a strict diet, and lost 10 pounds. On November 17, 1980, I had a cerebral hemmorhage and nearly died. I spent 18 days in New York Hospital. Since then, my memory and my hearing have deteriorated and my coordination is very poor. Worst of all, I have trouble with words, often saying hot when I mean cold, or house when I mean hotel. Sometimes whole sentences come out the wrong way.

However, I feel I am one of the lucky ones as I can still function fairly well on my own.

Unfortunately, as long as these pills are readily available, no amount of warnings will stop people from taking what seems like an easy way to lose weight. I have friends who, in spite of what happened to me, are still taking Dexatrim, confident it won't happen to them. In spite of all my warnings about them.

These diet pills are dangerous and should be taken off the market.

Mr. **Pepper**. Well, thank you very much, Ms. Sachs.

Next is Mrs. Gloria Jean Davis of Albany, Ga.

Mrs. Davis, speak right into the microphone, please, ma'am.

STATEMENT OF GLORIA JEAN DAVIS

Mrs. **Davis**. My name is Gloria Davis. I am a resident of Albany, Ga. I am 32 years of age. I have four children. I am divorced from my husband.

Lillie Thornton Zackery will read my statement.

Ms. **Zackery** [reading]:

> In May of 1978 I decided to try and lose some weight. I went to a local store and purchased some over-the-counter diet pills to assist me in losing weight. I went back home, read the directions that came with the diet pills called appedrine and took some pills that day pursuant to the directions. Shortly after taking the pills I developed a severe headache. My family rushed me to a local hospital where I passed out. The doctors diagnosed my condition as a stroke. The doctor asked my mother, whom I lived with at the time, whether or not I had taken any medicine. She said, "No, except for the diet pills."
>
> After seeing the diet pills that were taken to the doctor's, upon their request, the doctor said that they were certain that the diet pills caused my blood pressure to go up extremely high, thereby causing the stroke. Prior to taking the diet pills, I was in excellent health and was taking no medicine of any kind, whether prescriptive or non-prescriptive. I have never had high blood pressure in my life prior to the stroke.
>
> After the stroke I was in the intensive care unit at the hospital for 2 months and then in a wheelchair for the following 6 months. Although it has been approximately 5 years since the stroke, I still have little use of my right arm and leg. The doctors say my condition is permanent.
>
> Before the stroke I was employed but now I cannot work due to my physical condition caused by the stroke. I did sue the company which produces this diet drug, and won my case. However, others will not be as fortunate as I was.

Mr. **Pepper**. Thank you very much, Ms. Davis. We are sorry that you have experienced that tragedy.

Next is Mrs. Janey Phipps, a registered nurse of Gray, Ky.

STATEMENT OF JANEY PHIPPS

Ms. **Phipps**. Thank you, Mr. Chairman.

I am a registered nurse and I work in a coronary care, intensive care, unit, and I've worked in this unit for 4 years.

Two and a half years ago, after the birth of my second child, I wanted to lose some weight. Subsequently, I began to take an over-the-counter appetite suppressant known as Dietac. Before taking this preparation I read the label of ingredients, noting that this particular brand contained a drug known as phenylpropanolamine hydrochloride, known as PPA.

Dietac, the particular brand that I took, contains 75 milligrams of the PPA per timed release capsule. I also noted the warning on the package cautioning people with heart disease, hypertension, diabetes, and thyroid disease not to take the preparation. I considered myself a healthy person, having none of the above-mentioned afflictions and therefore began to take the drug, as directed, one capsule daily.

On the fourth day of my diet regimen I began to feel unusually and intensely fatigued. I decided to lie down and relax. In doing so I felt so fatigued that I actually ached all over. I became aware of an odd feeling of slow pounding in the center of my chest and soon realized the general body aches coincided with each slow pulsation. I soon realized that the pulsation I was experiencing was, in actuality, my heart rate. I counted my radial pulse, that's the one that one feels in the wrist, and it was 40, for 1 full minute. I had my hushand take my pulse and he also counted 40 beats per minute.

I became very concerned about this rate and counted my heartbeat with my stethoscope, and it was still 40. I then realized that something terrible was happening to me. I went to the hospital and was admitted to the same coronary care/intensive care unit where I worked. I was placed on the cardiac monitor that showed my heart was only beating 36 to 40 times per minute. This condition is known as sinus bradycardia.

My blood pressure was extremely elevated, being 200 over 120. At that point I realized two distinct dangerous possibilities. First of all, that the electrical conduction system in my heart could become further arrhythmic and I could die. Second, I could have a stroke. I remember having thoughts of denial and disbelief that even this could happen to me.

My physician, Dr. Glen Baker, was called to see me. He prescribed intravenous atropine sulfate to increase my heart rate. After receiving the atropine sulfate, my heart rhythm changed from the aforementioned sinus bradycardia to a junctional rhythm. This means the electrical impulse that normally begins in the sinus or sinoatrial node in the heart had been taken over by the atrial ventricular node in the heart. This heart rhythm is not a normal conduction pathway.

I remained in this heart rhythm for several minutes and my blood pressure remained elevated. I was fully alert and aware of everything that was happening to me. After the junctional rhythm, my heart rate increased and converted to sinus tachycardia, a normal conduction pathway, except the heart rate is greater than 100 beats per minute. Gradually, my heart rate slowed to a normal sinus rhythm and my blood pressure returned to normal. The question was what caused these problems.

I told my physician the only drug I was taking at the time was the Dietac preparation. He immediately suspected the PPA caused my blood pressure to elevate. But why did I have a slow pulse? Normally, the PPA would cause a fast pulse or tachycardia.

I stayed in the hospital for 3 days, undergoing various tests, all of which were normal. I also saw a cardiologist. The slow heartbeat, my physician explained, was caused from excessive pressure on my carotid arteries during the hypertensive episode. The carotid arteries, located in the neck, are very pressure sensitive, and when stimulated cause a slowing of the heartbeat. This is due to the stimulation of the parasympathetic nervous system, a division of the autonomic nervous system.

I assumed that because a drug is sold over the counter and not by a prescription, that a drug is safe. How many other people, particularly the elderly, also believe this assumption? The older individual, who statistically stands to have hidden heart disease and hypertension are at great risk when taking over-the-counter preparations containing the PPA. If something like this can happen to a healthy, young individual like myself, it can happen to anyone.

Mr. **Pepper**. Thank you very much, Ms. Phipps. You've heard the signals here and you see the signs indicating there is a vote on the floor. And we will have to take a temporary recess until we can run over and vote. Then we'll be right back.

[Brief recess.]

Mr. **Pepper**. The committee will come to order, please.

Our next witness will be Mrs. Kathleen O'Reilly, consumer expert of the National Broadcasting Co., and an experienced lawyer in this field. Mrs. O'Reilly, we are pleased to have you here today.

STATEMENT OF KATHLEEN O'REILLY

Mrs. **O'Reilly**. Thank you, Mr. Chairman. Last October 27 the NBC "Today Show" aired a segment on PPA and diet pills, and a copy of the transcript of that segment will be provided for the record, but with the hope that we don't have any mechanical problems, we will show that excerpt now.

Mr. **Pepper**. Is this it?

Mrs. **O'Reilly**. Yes.

Mr. **Pepper**. Oh, good.

[Videotape shown.]

Announcer. The drug industry sells 10 billion diet pills a year, but there's a growing controversy over whether these non-prescription diet pills work and whether they're safe. With us is consumer expert, Kathleen O'Reilly.

Mrs. **O'Reilly**. The main active ingredient in diet pills is phenopropanolamine, PPA for short. It's PPA in small doses which generally is taken as a decongestant. But according to consumer groups, a much higher dose of PPA in diet pills is neither effective, nor safe, especially for consumers with high blood pressure or hypertension, the very consumers who are often overweight.

This diet pills box says to use up to 3 months. The diet pill ads often speak of danger for a longer period, 27 weeks, 20 weeks, 36 weeks. The average weight loss, according to Science in the Public Interest is only in the first few weeks, for a total of about four pounds.

Voice. Studies conducted by Thompson Medical itself have shown that the expected weight loss can be anywhere from a third to a half a pound a week.

Mrs. **O'Reilly**. What about the safety of PPA? It's ill-advised for people with high blood pressure, heart disease, diabetes, thyroid, kidney or other diseases, and has been linked to strokes, cerebral hemmorhages, and other cardiovascular disorders.

Since 40 percent of those who are overweight do suffer from hypertension and related medical problems, and even more are borderline, the Center for Science in the Public Interest has warning language to be included in all ads, since overweight consumers are most vulnerable to PPA's adverse potential.

Industry claims that warnings on the box are sufficient, and that the Food and Drug Administration has approved PPA.

Voice. They have found that with hundreds of thousands of doses being taken on a daily basis that there is a very small, negligible, incidence of adverse reactions and they have, therefore, found that the product is safe and effective.

Mrs. **O'Reilly**. Is that the FDA's position?

Voice. Not really, no. As a matter of fact, the Food and Drug Administration has not put forth its policy with regard to the safety and effectiveness of these drugs to date. What we did was to publish the report of an expert advisory panel. We have expressed some concern about the panel's recommendations for dosages of phenylpropanolamine and, as a matter of fact, we dissented from the panel recommendations to increase the dose that's already in use out in the marketplace.

Mrs. **O'Reilly**. Frank O'Donnell of Milwaukee had no medical history suggesting a potential problem with PPA and says he took the diet pills as directed. But yet he suffered a stroke.

Mr. **O'Donnell**. Well, I had a numbness in the back of my arm and numbness in my face, and those are the permanent result of the stroke.

Mrs. **O'Reilly**. Cut down on calories, increase exercise, common sense. That's the recommended way to lose weight safely. Does that include diet pills?

The Food and Drug Administration has recently expressed concern about the safety of PPA and will, within a year, decide whether or not these drugs should be banned or otherwise restricted.

Two years ago the Federal Trade Commission staff recommended legal action against the manufacturers of these products, but still no formal action has been taken.

Dr. Thaddeus Krout, a medical expert in the field of PPA:

Dr. **Krout**. The tragedy is that this relatively useful agent for decongestion is now abused by the false advertising which has been brought forth by the companies that want to make a great deal of money out of this whole situation.

Mrs. **O'Reilly**. Whether or not the government takes action on this issue of PPAs remains to be seen in the next few months. We will be watching it. In the meantime people are becoming very suspicious of other over-the-counter drugs. We're going to be talking about the tampering problem.

[End of videotape excerpt.]

Mrs. O'Reilly. I would now like to highlight for you the major objections to that piece that were raised by Thompson Medical, and describe the legal and scientific basis which did support this segment.

First, Thompson Medical objected to the language that said, "It's PPA in small doses that's generally safe as a decongestant, but according to consumer groups, the much higher dose of PPA in diet pills is neither safe nor effective." It was Thompson Medical's contention that the facts are just the opposite. The dosage permitted by the Food and Drug Administration in decongestants is 150 milligrams per day, while the permissible dosage in over-the-counter appetite control pills is only 75 milligrams per day.

Our response is that the higher dosage for decongestants, cough remedies, and the like, reflects the fact that these cold remedies are typically taken for only a few days at a time, whereas diet pills are taken for weeks and months at a time and thus have scientifically significant, cumulative effects. And as we have heard today, those cumulative effects are particularly relevant for the elderly, who are taking many more medications, both over the counter, and prescription, than the population as a whole.

It is also a reflection that the higher long-term concentration of diet pills has raised the safety questions at the Food and Drug Administration.

Although the FDA advisory panel had recommended raising the permissible dosage in appetite control pills, the FDA specifically rejected that recommendation, and we will submit to you the Federal Register announcement on that.

And they also had expressed concern that the diet pill packages do not universally include language alerting consumers to the problem of taking diet pills in addition to taking other products that contain PPA, which is an additional medical risk.

Thompson Medical also objected to that statement in the script that said the consumer groups were questioning the efficacy and the safety of PPA and diet pills. It was Thompson's contention that all evidence shows that PPA in diet pills is effective and safe.

We pointed out to them the number of scientific studies that have been printed in the Federal Register, including the summary, pointing out safety problems involved with PPA in diet pills. We also pointed out that if there were no safety questions, why do the FDA regulations specifically state that all marked drug products containing PPA bear or contain a statement warning against use by individuals with high blood pressure, heart disease, diabetes, or thyroid disease.

We also pointed out that in the leading case of *Porter* v. *Dietsch* the seventh circuit upheld a Federal Trade Commission order requiring a manufacturer of diet pills containing PPA to include such a health warning. Indeed, most of the diet pill packages do contain such a warning, and Dr. Ekien, who was interviewed on camera, who is the head of the proprietary association, stated that, on camera, "All manufacturers are in the process of including such a warning." Dr. Ekien did not state or hint that such a warning would be unreasonable.

Thompson Medical also objected to that part of our segment which stated that the diet pill box says, "Use up to 3 months," but the diet pill ads often speak of dangerous longer periods. Thompson's contention was that there is no evidence that longer use is either dangerous or unsafe.

Both the Federal Trade Commission spokesperson, Amanda Peterson, and the FDA spokesperson, Dr. Halperin, expressed concern on camera about this very issue. Under FDA procedure, the burden of proof is on the drug manufacturer to demonstrate the safety and efficacy of a drug, and as Dr. Halperin explained, FDA does not conduct its own scientific studies. It evaluates the studies which are initiated and paid for by industry.

The diet pill industry had not submitted studies involving more than the 12-week limit. With this as a background, it is important to note that under the Food, Drug, and Cosmetic Act, drugs are only legally safe when used in dosage manner, or with a frequency or duration described or recommended in the labeling. The duration prescribed and recommended on the labeling of diet pills is "Up to 3 months." Thus, usage beyond that period cannot legally be characterized as safe and caselaw supports that principle, the leading case being *The Pharmaceutical Manufacturers Association* v. *Richardson*.

Even Dr. Ekien said that the 12-week period is not meaningless, and he expressed manufacturer concern over the abuse of these drugs, and in no way attempted to refute the wisdom of that duration limit, explaining that the pills were to be used temporarily as an adjunct to an overall program of weight control.

As to the question of efficacy, Thompson Medical contends that on the basis of 14 clinical studies, the average weight loss on PPA is over 1 pound per week for a considerably longer period of time than described in our segment. We pointed out that scientific studies show that people lose weight even with a placebo and these double blind studies are routinely used to evaluate real weight loss. Indeed, the FDA panel had specifically rejected a Thompson Medical study because it was not a double blind study, and had recommended double blind studies as the protocol to be used.

Under this commonly accepted scientific procedure, the placebo weight loss subtracted from the product-associated weight loss is used to arrive at what is arguably called "the real weight loss attributable to the tested product." That is the reason the Thompson studies, which do not discount for the placebo effect, are different in their results from the studies which use the scientifically-accepted method of double blind.

Thompson Medical also contended that Bruce Silverglade of the Center for Science in the Public Interest's statement that studies conducted by Thompson Medical Co. itself have shown that the expected weight loss can be anywhere from one-third to one-half pound per week, were inaccurate. We have provided these scientific studies on which Mr. Silverglade's comments were made.

Also, Thompson Medical objected to that part of the script that said PPA has been linked to strokes, cerebral hemmorhages, and other cardiovascular disorders. This is significant in that Thompson contends that no causal relationship has ever been established.

The script language is the verbatim cautionary language included on the diet pill box labels. But it is not yet contained in the ads, despite the Porter-Dietsch decision, and that is the basis of the petition by the Center for Science in the Public Interest. It's important to understand the terminology "causal relationship" is not the FDA legal standard.

For example, the recent bans regarding Ora-Flex and starch blockers were based on the traditional standard of linked or associated-with health problems, and the Center for Science in the Public Interest had submitted for the record a variety of the examples of that link.

Finally, the whole notion of whether or not there is a suggestion that industry is claiming that the Food and Drug Administration has approved PPA. In the script you saw that Dr. Ekien from the proprietary association made that comment. It was Thompson Medical's contention that that had been taken out of context, that he was only talking about the U.S. FDA panel.

I will submit the extensive, word for word, interview with Dr. Ekien and you will see that he was specifically talking about the FDA, apart from the U.S. panel. I read, for example, my question to him was: "Has the FDA itself found PPA to be safe and effective for over-the-counter use?" His response:

> The FDA has issued a tentative proposal with respect to PPA which they have not dissented from the panel's recommendation. That is tantamount to their saying at this point, giving an okay to this molecule.

I think most important of all is the fact that in June of last year the National Advertising Division of the Council of Better Business Bureaus, which is the self-regulatory mechanism of the advertising industry, reported that Smith, Klein, Beckman Corp., manufacturers of Dietac Maximum Strength diet aid capsules, had withdrawn its advertising claims pursuant to a National Advertising Division challenge.

In that report, NAD states, and I quote, "Additionally, the National Advertising Division felt that reference to a quote, 'U.S. government advisory review panel', end of quote, implied official endorsements by the government itself." Not only is this industry watchdog conclusion consistent with our script narrative; Dr. Ekien himself was explicit in that respect.

Finally, the issue of whether or not the fact that the FDA has recently expressed concern about the safety of PPA and will, within a year, according to Dr. Halperin, and that quote came from last September 20, decide whether or not these drugs should be banned or otherwise restricted. It was Thompson's contention that this falsely implies that PPA is dangerous and that FDA will either ban or restrict its use.

What the FDA has actually done, however, is merely to have included this drug under its continuing review of all over-the-counter products. We pointed out to them the specific concerns raised in the Federal Register by the FDA went way beyond the aspects of continuing review and supplied those studies as well.

So, I hope that this may be instructive in responding to the major substantive contentions that Thompson Medical had raised on the basis of this segment.

Thank you.

Mr. **Pepper.** Thank you very much, Mrs. O'Reilly.

Did you want to make a statement?

Mr. **Adamo.** Yes.

Mr. **Pepper.** Well, could you wait and let us take it in a little more orderly way? We have this panel here and it's customary, now, to allow questioning of the panel by members of our committee.

Oh, I'm sorry. I understand from the staff that you should be heard, sir. Go right ahead. You were one of those who were supposed to be on the panel. I'm sorry. We just didn't have room for you.

Mr. **Adamo.** My name is Frank Adamo.

Mr. **Pepper.** Mr. Adamo, we are pleased to have you.

Mr. **Adamo.** Thank you very much.

Mr. **Pepper.** We're glad to hear your statement.

Mr. **Adamo.** I'm pleased to be here.

STATEMENT OF FRANK ADAMO

Mr. **Adamo.** I do recognize that the hearing on the safety of PPA usage is being held through the Select Committee on Aging, and is concentrating primarily on those PPA-related cases involving older people. However, I believe that the problems caused by PPA usage cut across all age groups and to disregard an episode based on my age would be doing a disservice in your efforts to determine whether or not PPA is, indeed, safe and effective, as advertised.

In October 1980 I began using Dietac diet medication. I chose Dietac because it is manufactured by the same company that produced a well-known cold medication, and the advertisements I heard convinced me not only of the safety of the product but of the effectiveness as well.

I followed the label directions, taking one time release capsule a day, each containing 75 milligrams of PPA, and 200 milligrams of caffeine. I was on no other medication at the time.

On January 19, 1981, while at work, I suffered a stroke. Hospitalization and a battery of tests revealed an area of damage to the blood vessels in the right side of my brain. Because I was healthy and had no history of medical problems, my doctor was puzzled as to the cause. I was 28 at the time.

My doctor put me on blood thinning medication in an attempt to prevent any further episodes.

On October 19, 1981, I heard a report on the radio linking PPA usage with a variety of medical problems, including high blood pressure, personality changes, and strokes. I got in touch with the Center for Science in the Public Interest, who had released that report. The more information I received, the more convinced I became that my stroke was caused by PPA ingestion. I related all the information I could obtain to my doctor. Although he would not commit himself to a direct link between PPA and my stroke, after reviewing the information he felt confident enough in the possibility of a link to take me off blood thinning medication. I have not experienced any further problems since my stroke, when I stopped taking Dietac and avoided any products containing PPA.

When I consider all of the possible effects I could have suffered from having a stroke, I feel extremely fortunate that I don't have any of the obvious physical problems or disabilities resulting from my episode. But there are those who have suffered even more serious and permanent results from PPA ingestion, and I can't help but wonder how many more people have suffered various medical problems and are unaware that the cause was PPA ingestion.

What happened to me and to the many other victims should never have occurred. Despite the advertisements to the contrary, I feel that PPA has been shown to be a very unsafe and dangerous drug and further, I believe that the FDA has an obligation to protect the safety of the American public, particularly any potential future victims, by prohibiting the use of PPA in any and all over-the-counter medications.

Thank you very much.

Mr. **Pepper**. Well, thank you very much.

Ms. Ferraro, would you care to make any statement before we start questioning the witnesses?

Ms. **Ferraro**. No, Mr. Chairman. I'm just delighted that you're having these hearings. I have participated with you in the joint hearings that we had with the Senate and I look forward to picking up on the testimony of the witnesses.

Mr. **Pepper**. Thank you very much.

I'm very sorry that I've got to go to another meeting, and I'll ask Ms. Oakar if she'll preside. And now you will proceed to question the panel.

I want to thank each one of the panel this morning for your excellent statements and for your coming here to help us in this inquiry. We're just trying to ascertain the truth for the protection of the elderly people of this country. And I want to thank all the other members of the excellent program that we have here today, and I'm sorry that I'm not going to be able to hear you, but I hope to be able to read the record. Maybe I can get back a while later.

Ms. Oakar.

Ms. **Oakar**. Mr. Chairman, I want to submit for the record correspondence between Congressman James Florio and the FTC regarding advertisements for diet pills. I think that this is especially important in light of the fact that on a particular box of diet pills the language used to lure people to buy the product is three-fourths of an inch high compared with the less than one-sixteenth of an inch print used to describe the warning and caution caption. This lures the consumer to these unsafe products.

[The material submitted by Representative Oakar follows:]

U.S. House of Representatives
Subcommittee on Commerce, Transportation, and Tourism
of the
Committee on Energy and Commerce
Washington, D.C. 20515

February 24, 1982

AL COUNSEL
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The Honorable James C. Miller, III
Chairman
Federal Trade Commission
Room 440
6th & Pennsylvania Avenue, N. W.
Washington, D. C. 20580

Dear Chairman Miller:

Advertising claims regarding the safety and effectiveness of over-the-counter (OTC) diet pills containing phenylpropanolamine have received particular attention in recent years.

In 1977, the FTC, recognizing problems with manufacturers' claims for such products, ordered producers to cease and desist from deceptive advertising claims and to include a health warning in all future advertising. It has been brought to the Subcommittee's attention that subsequent and substantial violations of the 1977 order have occurred, thus prompting staff of the Bureau of Consumer Protection to recommend in late 1980 that civil penalties be appropriately assessed against certain firms. However, no action has been taken on these recommendations.

I would like to know the status of any review of diet pill advertising, the disposition of the staff recommendations to assess civil penalties, and the FTC's current policy with regard to the regulation of diet pill advertising.

Your attention to these matters is appreciated.

Sincerely,

J.J. Florio

James J. Florio, Chairman
Subcommittee on
Commerce, Transportation and Tourism

JJF:rfs

FEDERAL TRADE COMMISSION
WASHINGTON, D.C. 20580

BUREAU OF
CONSUMER PROTECTION

MAR 25 1982

The Honorable James J. Florio
Chairman
Subcommittee on Commerce,
  Transportation and Tourism
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

Dear Mr. Florio:

Chairman Miller has requested that I answer your February 24, 1982, letter concerning advertising for over-the-counter diet aids containing phenylpropanolamine hydrochloride (PPA). I understand that you are concerned that current advertising for PPA diet aids may be deceptive and contrary to the holding of our recent *Porter and Dietsch* case. 90 F.T.C. 770 (1977), *modified*, 605 F.2d 294 (7th Cir. 1979), *cert. denied,* U.S. 950 (1980), *amendments to order,* 95 F.T.C. 806 (1980).

In *Porter and Dietsch* respondents were ordered to disclose in future advertising for a PPA-containing diet aid, X-11, that the product should not be used without medical supervision by persons with hypertension, heart disease, diabetes or thyroid disease; and to disclose that successful use of the product requires dieting. At the same time the advertisers of X-11 were ordered to stop making unsubstantiated exaggerated weight loss claims. The FTC reasoned that the clinical evidence relied on by respondents that showed no more than a fraction of a pound of weight loss per week on the average was insufficient to substantiate a claim that consumers experience dramatic weight loss as a result of using X-11.

In your letter you advise Chairman Miller, "It has been brought to the Subcommittee's attention that subsequent and substantial violations of the 1977 order have occurred, thus prompting staff of the Bureau of Consumer Protection to recommend that civil penalties be appropriately assessed against certain firms." The FTC Act permits us to seek civil penalties or other redress for violation of the FTC Act in two situations: (1) where *the named respondents* have violated a final adjudicated or consent order against them, and (2) where *any party* has knowingly violated a final order resulting from a *fully litigated* Commission adjudication.

To our knowledge, the named respondents in Porter and Dietsch have been in substantial compliance with the order against them. With respect to other parties, who were not named in the Porter and Dietsch case, they cannot be in violation of the order until they know the acts or practices that are prohibited by it. The Commission practice is to adopt a formal synopsis of the case and serve it, along with a copy of the FTC opinion and order, on the pertinent industry members. Thereafter, any industry member who continues to engage in the proscribed acts or practices is in violation of the FTC Act and may be sued for civil penalties or other redress.

At the time that I became Bureau Director in October, 1981, a staff recommendation was pending that the FTC adopt and serve a synopsis based on the Porter and Dietsch case. After reorganizing the Bureau and dealing with several budget and reauthorization matters, I made this matter one of my priorities. I am considering in conjunction with certain diet aid advertising whether to serve a synopsis of Porter and Dietsch. I anticipate that in a short time I will reach a final decision on whether this synopsis is necessary, and if so what it should include.

I hope this addresses your concerns and those of your Committee.

Sincerely yours,

Timothy J. Muris
Director

[illegible]
3/22/82

U.S. House of Representatives
Subcommittee on Commerce,
Transportation, and Tourism
of the
Committee on Energy and Commerce
Washington, D.C. 20515

August 9, 1982

GENERAL COUNSEL
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CONGRESSIONAL

The honorable James C. Miller, III
Chairman, Federal Trade Commission
Room 440
6th & Pennsylvania Avenue, N. W.
Washington, D. C. 20580

Dear Chairman Miller:

This is in further reference to our correspondence concerning over-the-counter diet pills containing phenylpropanolamine. In my letter of February 24, 1982, I requested a report on the status of the Commission's review of diet pill advertising. By letter of March 25, 1982, the Director of the Bureau of Consumer Protection, Mr. Timothy J. Muris, noted my concern that current advertising for diet pills may be contrary to the holding in the Porter and Dietsch case. Mr. Muris stated that he had made this issue a priority matter and expected to reach an early decision on whether to proceed under the Commission's Section 5(m)(1)(B) authority. I understand that other enforcement options might also be available.

With the passage of over four months since Mr. Muris' letter to me without further indication of activity, I am writing again to inquire as to the status of your action and the reason for delay. Since this matter involves allegations of serious public health hazards, including strokes experienced by those using diet pills, the possibility of ongoing flagrant violations of the laws administered by the Commission is of grave concern to me. In this regard, press reports have been called to my attention which suggest that overall, the enforcement activity of the Commission in recent months has been drastically reduced. While I would not necessarily credit these reports without further substantiation, I am concerned that the diet pill matter may reflect some even more fundamental underlying administrative difficulty of which the Congress has not been apprised.

I look forward to hearing from you on this matter.

Sincerely,

J. J. Florio

James J. Florio, Chairman
Subcommittee on
Commerce, Transportation and Tourism

JJF:pjs

JAMES J. FLORIO, N.J., CHAIRMAN

BARBARA A. MIKULSKI, MD
W. J. "BILLY" TAUZIN, LA
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(EX OFFICIO)

U.S. House of Representatives
Committee on Energy and Commerce

SUBCOMMITTEE ON COMMERCE, TRANSPORTATION, AND TOURISM

CHIEF COUNSEL AND STAFF DIRECTOR

Washington, D.C. 20515

April 14, 1983

GENERAL COUNSEL
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CONGRESSIONAL

The Honorable James C. Miller, III
Chairman
Federal Trade Commission
6th and Pennsylvania Ave., N.W.
Washington, D. C. 20580

Dear Chairman Miller:

I have received a letter of April 12, 1983, from Timothy Muris of your staff, enclosing a copy of the synopsis of the Porter & Dietsch decision.

As you know from our prior correspondence, I have had a long-standing concern regarding this matter. I remain troubled by the extended time it took for the FTC staff to bring this matter to the Commission for decision.

Additionally, the synopsis raises a number of new questions in my mind. First, while Mr. Muris' letter states that the synopsis has been released, it does not say that it has been served. Please advise me when such further action may be contemplated. Second, it appears to me that there may be a number of problems relating to the promotion of over-the-counter diet aids containing PPA which are not addressed by the synopsis. While the Commission may have decided not to pursue these matters under its section 5(m)(1)(B) authority, I trust that the appropriateness of other enforcement initiatives will be considered promptly. Given the indications of the widespread advertising of diet aids containing PPA and the potential adverse effects on consumers, further delay is unwarranted and could raise serious questions about the commitment of the Commission to protection of the consuming public.

I appreciate your keeping me advised on the progress of this matter.

Sincerely yours,

JJ Florio

James J. Florio, Chairman
Subcommittee on
Commerce, Transportation and Tourism

JJF:pjw

FTC news

Federal Trade Commission ***Washington, D.C. 20580***

FOR IMMEDIATE RELEASE: April 1, 1983

FTC OUTLINES UNACCEPTABLE ADVERTISING FOR SOME WEIGHT-CONTROL PRODUCTS, PLANS

The Federal Trade Commission today described what it considers to be deceptive advertising for some weight control products and plans. The Commission's goal is to ensure that marketers of weight control products and plans are aware of the provisions of a 1977 FTC order against Porter & Dietsch Inc. That company's product contains the appetite suppressant phenylpropanolamine hydrochloride.

The FTC notice -- called a synopsis -- outlines key aspects of the Commission's Porter & Dietsch decision. It reminds the industry that an advertiser must have a reasonable basis for claiming a product or plan will bring about weight loss. Also, a claim of scientific support for a statement about such a product is deceptive if the evidence is not competent or does not fully support the statement at the time it is made.

Along with these provisions, the Commission pointed out it is unlawful to claim that a weight control product contains a unique ingredient, unless that ingredient is absent from other available weight control products. And the Commission also cautioned against the use of testimonials misrepresenting directly or indirectly that any particular experience with a weight control product or plan reflects a typical experience.

Copies of the synopsis are available from the FTC's Public Reference Branch, Room 130, 6th Street and Pennsylvania Avenue N.W., Washington, D.C. 20580; 202-523-3598; TTY 202-523-3638.

# # #

MEDIA CONTACT: Janet Bass, Office of Public Affairs,
202-523-1848

STAFF CONTACT: Susan Elliott, Bureau of Consumer Protection,
202-724-1499

(Docket No. 9047)

[Porter]

SYNOPSIS OF FEDERAL TRADE COMMISSION DETERMINATIONS CONCERNING PROMOTION OF PRODUCTS AND PLANS FOR WEIGHT CONTROL*

Porter & Dietsch, Inc.
Docket 9047

This synopsis has been prepared for purposes of 15 U.S.C. §45(m)(1)(B), a law which provides for civil penalties for certain violations of the Federal Trade Commission Act. The Federal Trade Commission has determined that the following acts or practices are deceptive and are unlawful under Section 5(a)(1) of the FTC Act, 15 U.S.C. §45(a)(1).

A. It is deceptive to represent, directly or by implication, that use of an appetite suppressant, and/or methylcellulose, enables a person to lose body weight or fat without dieting or restricting his or her accustomed caloric intake.

B. It is deceptive to represent, directly or by implication, that a weight control product contains a unique ingredient or component, unless the ingredient or component is not present in other available weight control products.

C. It is deceptive to represent, by means of testimonials, directly or by implication, that any particular experience with a weight control product or plan reflects the typical or ordinary experience of users of the product or plan, unless the representation is true.

D. It is deceptive to represent, directly or by implication:

1. that use of a weight control product or plan will result in loss of body weight or fat, without possessing and relying upon a reasonable basis for the representation at the time it is disseminated;

2. that scientific evidence supports a statement about a weight control product or plan, without possessing and relying upon competent scientific evidence that fully supports the statement at the time the representation is disseminated.

Approved:

Resolution: Approved in File 802 3132
Marketers of Weight Control Products and Plans

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* As used here, "weight control" includes the reduction or elimination of fat with or without weight loss. This synopsis is based on the Commission's Porter & Dietsch decision. The decision was approved, with a few changes, by a federal appeals court. A further appeal to the U.S. Supreme Court was turned down. The legal citation for the case is 90 F.T.C. 770 (1977), modified, 605 F.2d 294 (7th Cir. 1979), cert. denied, 445 U.S. 950 (1980), amendments to order, 95 F.T.C. 806 (1980).

Ms. **Oakar**. This is a problem that affects the elderly as well as younger people. It cuts across age groups, although the elderly with all their problems of older age have more tendencies toward high blood pressure, et cetera. I want to submit a computer printout which indicates that over 1,000 people have reported adverse reactions to PPA recently, and a third of them were over 55.

This printout from the Food and Drug Administration records 1,040 reported adverse drug reactions to products containing PPA. Thirty percent—313—of the reported cases were from persons over 55. The reactions range from headache to stroke to kidney failure. Forty percent of the reports of cardiovascular problems were from those aged 55 years or older.

[See app. 2, p. 259 for material submitted by Representative Oakar.]

Ms. **Oakar**. Dr. Wolfe, you mentioned that of the over-the-counter drugs that the FDA has checked out, two-thirds of them proved unsafe and ineffective?

Dr. **Wolfe**. One-third of the top-selling over-the-counter drugs, almost one-third, have ingredients which the FDA believes lack evidence of safety and effectiveness.

Based on our own review, when we sent this information all over the country to various medical experts on colds and stomach problems, we would add another third. One of the biggest ingredients in the second third, the one that FDA thinks is safe and effective but which we don't, is PPA, phenylpropanolamine. There are a lot of other ingredients. So that when you add this up, what we're talking about is that of the best-selling products in the country, the top 466 drugs, two-thirds of them, slightly over two-thirds, contain ingredients which the FDA or our experts or both, think lack evidence of safety, effectiveness, or both.

Ms. **Oakar**. Well, if this is true in so many over-the-counter drugs that are sold not only in drugstores, but in grocery stores and all kinds of little outlets——

Dr. **Wolfe**. Airports.

Ms. **Oakar** [continuing]. Airports, where pharmacists or no one with an insight into the medical background is around, what should be done about those that have already been proven unsafe and ineffective? Should we make them prescription drugs? My bill addresses the gap that Cathy mentioned in terms of over-the-counter drugs, the fact that it's voluntary to report adverse reactions on the part of the drug industry. But what would you suggest we do for the American public?

Dr. **Wolfe**. Well, one symptom about what should be done can be seen, as you mentioned earlier, in the FDA not showing up. We are currently in the U.S. Court of Appeals here. We have filed suit against the FDA because we believe that the 1962 drug law which, as you mentioned, requires proof of effectiveness, and which is now 21 years old, is being rampantly violated by the fact that all of these drugs, with ingredients lacking evidence of effectiveness, are still on the market even though as long as 6 or 7 years ago panels of experts called in by the FDA found many of them to be lacking evidence of effectiveness or safety.

The outcome of this lawsuit is certainly one thing which might push the FDA. We won or at least settled favorably a similar lawsuit on prescription drugs where, again, we were arguing that the FDA was violating the 1962 drug effectiveness law in allowing hundreds of prescription drugs, also lacking evidence of effectiveness, to be on the market.

The remedy which the FDA settled out of court was to add more staff, not very complicated, to set some deadlines, and to put top priority on the drugs that were the biggest sellers, instead of just the opposite, which was going after the small guys and then waiting on the bigger ones because they had more lawyers in Washington.

We would hope the same kind of tight time schedule, increased staff, whatever else, might occur for the over-the-counter drugs. Otherwise, people are really getting defrauded. As I said, one-third of the top-selling drugs have such ingredients. But if you look at just the ingredients alone, because the FDA review really doesn't look at products; it just looks at ingredients, fewer than one-fourth of the ingredients which have been reviewed are safe and effective for their intended uses, and that's why, as I mentioned earlier, in many ways we are still back in the snake oil days.

If anything, we're worse off in the sense that instead of a little wagon called "the medicine show" which only reaches as many people as can crowd around it, we have television which is able, through false and misleading advertising such as has been mentioned this morning, to reach millions or tens or hundreds of millions of people with messages implying or stating explicitly things that aren't true. And the Federal Trade Commission is 10 years behind on many of these and, in some cases, hasn't done anything.

So, I think one remedy is really to push the Government agencies, the FDA and the FTC, to stop breaking the law. They are breaking the law. That's what we're arguing in the Court of Appeals here.

Ms. OAKAR. Thank you. Mrs. Sachs, thank you for coming. You indicated in your testimony, that you had a cerebral hemorrhage. Would you use the microphone? Thank you.

Mrs. SACHS. Yes, I did.

Ms. OAKAR. And you are still feeling the after effects of that difficult period?

Mrs. SACHS. Yes, I really am in many ways.

Ms. OAKAR. And what was your health like before you started taking diet pills?

Mrs. SACHS. It was extremely good. It was. You know, I needed to lose a few pounds, but nothing terribly bad. It's just that my son was getting married and I wanted to look good, and I thought I'd lose an extra 10 pounds. Before that my health was excellent. And I still don't have high blood pressure or any of the other illnesses.

Ms. OAKAR. You did not have any of the systems described on the back of the package, in that fine print?

Mrs. SACHS. Nothing. No.

Ms. OAKAR. It says if you have hypertension and any tensions like that you shouldn't take the drug.

Mrs. SACHS. Nothing like that, no.

Ms. OAKAR. Did you say you're 61.

Mrs. SACHS. I was then, yes.

Ms. OAKAR. How old were you when you took it?

Mrs. Sachs. I was 61 when I took the pills.

Ms. Oakar. When you took the pills?

Mrs. Sachs. Yes.

Ms. Oakar. Did your pharamacist recommend Dexatrim to you? He indicated that you ought to try this; is that right?

Mrs. Sachs. Yes, he did. Absolutely.

Ms. Oakar. I see. And he didn't ask your age or anything of that nature?

Mrs. Sachs. No, he didn't. And when I went back later and told him I had a cerebral hemorrhage, he just laughed the whole thing off.

Ms. Oakar. He laughed the whole thing off?

Mrs. Sachs. He said it must be inherited or it must be in the family. He wasn't going to admit anything.

Ms. Oakar. I would like to commend Howard Babbush and submit for the record the legislation he introduced to forbid over-the-counter diet pills from being sold to minors. I admire his courage. I understand that the legislative body was under pressure from the diet pill manufacturer—even though that manufacturer claimed that they did not want the pills sold to minors—who lobbied heavily to defeat the Babbush bill.

[Material submitted by Representative Oakar follows:]

STATE OF NEW YORK

807

1983-1984 Regular Sessions

IN SENATE

(Prefiled)

January 5, 1983

Introduced by Sens. BABBUSH, BARTOSIEWICZ, BERMAN, CONNOR, GALIBER, LAVALLE, MARKOWITZ -- read twice and ordered printed, and when printed to be committed to the Committee on Health

AN ACT to amend the public health law, in relation to the sale of phenylpropanolamine hydrochloride in diet pills or liquids

The People of the State of New York, represented in Senate and Assembly, do enact as follows:

Section 1. The public health law is amended by adding a new section thirty-three hundred eighty-four to read as follows:

§ 3384. Sale of substance containing phenylpropanolamine hydrochloride (phenylpropanolamine HCL). 1. It shall be unlawful for any pharmacy or other retail establishment to sell to any person under nineteen years of age any pills or liquids labeled as intended for dieting or weight loss which contain phenylpropanolamine hydrochloride (phenylpropanolamine HCL) unless, in the case of a pharmacy, it is duly prescribed by a licensed physician.

2. A violation of this section shall be a misdemeanor.

§ 2. This act shall take effect on the first day of September next succeeding the date on which it shall have become a law.

EXPLANATION--Matter in *italics* (underscored) is new; matter in brackets [ ] is old law to be omitted.

HOWARD E. BABBUSH
17 DISTRICT
ALBANY OFFICE
LEGISLATIVE OFFICE BUILDING
ROOM 804
ALBANY, N.Y. 12247
TEL. 518-455-[illegible]
DISTRICT OFFICE
[illegible] BROADWAY
ROOM 1002
NEW YORK, N.Y. 10007
212-587-[illegible]

THE SENATE
STATE OF NEW YORK

COMMITTEES
EDUCATION (RANKING MINORITY MEMBER)
—
BANKS
CODES
HEALTH
INSURANCE
JUDICIARY
SELECT COMMITTEE ON CRIME AND CORRECTION

MEMORANDUM

Senate # 807

AN ACT:

to amend the public health law, in relation to the dispensing of certain substances.

SUMMARY OF PROVISIONS:

This bill provides that over the counter diet pills and appetite suppressants can not be sold to a minor under the age of 18 without a doctor's prescription.

JUSTIFICATION:

Many school age children who may be unaware that they are hypertension victims, or who have a prior history of tachycardia, are buying over the counter diet pills, not for weight reduction, but to obtain the "high" that can be obtained by the high level of caffeine and other chemicals included in these compounds. In addition, these children repack the diet pills to resemble a prescription drug and sell them on the street to other minors who also use them to obtain a "high". The Federal Government is now investigating ways in which over the counter diet pills and other "look alikes" can be prohibited. In the interim, before comprehensive legislation can be developed, it is essential to restrict sales. At present, diet pills are as accessible as candy; but children and teens who use them to obtain a quick "high" may be putting themselves in serious danger. Because a comprehensive plan could be months or years away, this temporary solution is essential to protect minors.

FISCAL IMPLICATIONS:

None

EFFECTIVE DATE:

This act shall take effect on the first day of September next succeeding the date on which it shall have become a law.

Ms. Oakar. Let me ask Mrs. Davis, you were a stroke victim and I notice that you are still wearing a brace as a result. Is that as a result of the stroke that you had?

Mrs. Davis. Yes.

Ms. Oakar. And I have your doctor's testimony, who could not be here with you today. But did you have any health problems before you took diet pills?

Mrs. Davis. No.

Ms. Oakar. And your doctor wasn't aware of any?

Mrs. Davis. I had just had a baby about 6 weeks ago, and I was 26.

Ms. Oakar. But you had had your child.

Mrs. Davis. Yes.

Ms. Oakar. It does say on the package that if you are pregnant you should not take this. Now, what did you do? You appealed to the drug company and then when you got no satisfaction you took them to court? Is that what happened?

Mrs. Davis. No. My Congressman had wrote, you know, when I done wrote them I didn't get nothing from them. So I got my lawyer.

Ms. Oakar. And they settled out of court with you?

Mrs. Davis. Yes.

Ms. Oakar. Would you like to tell this committee how much you were able to get?

Mrs. Davis. $1,000—what was it?

Ms. Zackery. $125,000.

Ms. Oakar. But your health will never be the same, will it?

Mrs. Davis. No.

Ms. Oakar. I see.

Now, you attribute the problem you have now and the stroke that you had to these diet pills; is that correct?

Mrs. Davis. Yes.

Ms. Oakar. Thank you very much, Mrs. Davis. Ms. Phipps, you're a nurse. You gave us some technical-scientific data in your report. Did you go to a doctor when you noticed your heart beating so slowly?

Ms. Phipps. I noticed that my heart was beating very slowly and I went directly to the hospital.

Ms. Oakar. And what would you say actually happened to you?

Ms. Phipps. The way the physician explained it to me, that my blood pressure was elevated and the end result, it caused my heart to beat slower than normal.

Ms. Oakar. Kathleen, you gave us a tape. Did you have pressure placed on you as a result of your work as an investigative consumer advocate?

Mrs. O'Reilly. Personally? No. I did not.

Ms. Oakar. Did you have any threats of lawsuits or anything of that nature?

Mrs. O'Reilly. Not that I'm aware of. The legal points that I described were submitted by Thompson Medical to NBC and we responded to them.

Ms. Oakar. You have with you Mr. Adamo. We were a little remiss in not having you at the panel. Are you suffering? You're a reasonably young man. Are you suffering from any after effects as a result of the stroke you had?

Mr. **Adams**. Fortunately my residual effects are very slight in that I have numbness in the left side of my face and the back of my left arm. Those are permanent and, like I say, I feel very fortunate that I do not suffer with more serious and permanent types of reactions from my episode.

Ms. **Oakar**. Mr. Wortley? Thank you.

Mr. **Wortley**. Thank you, Madam Chairman.

I'd like to make an observation for Dr. Wolfe and Mrs. O'Reilly. In a recent edition of the International Journal on Obesity, an article entitled, "Three Controlled Trials of Weight Loss with PPA," indicates that patients taking PPA lost significantly more weight than those taking a placebo, 4.64 pounds compared to 2.07 pounds. In other words, that's about twice as much. Would you agree that this would seem to establish the effectiveness of PPA for losing weight?

Dr. **Wolfe**. Well, I don't think anyone said that PPA doesn't work at all over a short period of time. I don't know what article you're referring to or who paid for it or who did it, which makes a big difference in terms of evaluating it. But what has not been proven is the long-term effect over months and months, as is recommended by the company.

If people eat less, with or without PPA, they will lose weight. That is something that thousands of years have shown to be true. The question is long-term effectiveness and if you're taking it for a long time, the risks obviously increase over what they would if you were taking it for a short time.

As I say, I don't have the article. I don't know which one you're referring to.

Mr. **Wortley**. I have the article here. It came from the Medical College of Pennsylvania.

Dr. **Wolfe**. Who was it sponsored by? Does it say that? Who paid for the study?

Mrs. **O'Reilly**. And what is the date of it?

Mr. **Wortley**. April 13, 1982.

Dr. **Wolfe**. Mr. Wortley, I would be glad to look at the study and submit comments on it, if that's what you would like. Not at this moment because other——

Mrs. **O'Reilly**. A subsequent panel this morning of experts who are very familiar with the specifics of each of these studies, I'm sure will be able to respond to the points.

Mr. **Wortley**. So you think PPA is safe as an effective nasal decongestant? When it's used in a spray form?

Dr. **Wolfe**. In the book I mentioned this morning, "Over-the-Counter Pills That Don't Work," we discuss at some length the use of oral decongestants, whether it's PPA or phenylephrin or others, and the point we make is that first, if you've got a cold and you just have a runny nose, you shouldn't really use any kind of decongestant. If you really have a blocked up nose and might be at an increased risk of having an ear infection, for instance, especially if you're a child, it may make sense to use a decongestant.

Why take 50 times more decongestant, which you would take in an oral form, such as Contac, for instance, as opposed to taking one-fiftieth the dose in spray or nose drops? Nose spray and nose drops can't be used for more than 3 days or you can get side effects from them. But the point that was made earlier is that one thing which differentiates oral decongestants with PPA from the diet pills, is that you're going to use them for a much shorter period of time.

That is true. But we would add, why use them at all when you can use one-fiftieth the amount in a nose spray or a nose drop form, reduce the safety risks, if you only take it for 3 days, or less. Frequently people only need to use it for 1 day.

Mrs. O'REILLY. And our segment specifically recognized the generally accepted principle that PPA, used in a cough, cold remedy, and so forth, has generally been found to be safe and effective as a decongestant. And Dr. Prout, who you will be hearing from, who is acknowledged by the court, in the *Porter-Dietsch* case, as an established medical expert, could probably elaborate on that.

Mr. WORTLEY. We'll look forward to his testimony. I yield back the balance of my time.

Ms. OAKAR. Thank you. If I might just say for the record, the thrust of this hearing is on diet pills. We don't want to take Mr. Lantos' Contac pill away from him. Mr. Lantos?

Mr. LANTOS. Thank you very much, and I appreciate the Chair's assurance that I'll be able to take Contac in the future.

I sort of am interested in the anecdotal testimony that we have received from some of our witnesses, and obviously my reaction to them, as I take it everyone's reaction to them, is one of empathy and sympathy and concern and understanding. Each of you have had medical problems. There may or may not be a cause and effect relationship between your taking pills and your medical problems. But what I think is obvious, and I was particularly intrigued by your testimony, is that on the basis of your experience you are recommending that all over-the-counter medications be removed which have PPA, and I do not think that you have the qualifications to make such a judgment.

Dr. WOLFE. That is why I say it is my judgment.

Mr. LANTOS. Well, I understand that but there are 230 million people in this country and everybody has his judgments, and in various fields such as airline safety or the safety of drugs, we are dealing with experts. So, I would like to confine my questioning to Dr. Wolfe and to Mrs. O'Reilly, who I take it is an attorney?

Mrs. O'REILLY. That's correct.

Mr. LANTOS. You have no training as a physician?

Mrs. O'REILLY. I do not.

Mr. LANTOS. And you have no training as a scientist?

Mrs. O'REILLY. That's correct.

Mr. LANTOS. You have training as an attorney?

Mrs. O'REILLY. That's correct.

Mr. LANTOS. Having a daughter who is an attorney, I have high regard for your training in the legal field.

Dr. Wolfe, I'd like to ask you to address the question of obesity as a serious problem in the United States. The figures I have seen, and I have, as I always do, prepared myself for this hearing. The figures are in the neighborhood of 80 million Americans, depending on how you define obesity.

It's self-evident that a broad spectrum of problems, from cardiovascular diseases to cancer are related in varying ways and in varying degrees to obesity. Studies show that overweight individuals have a much higher likelihood of developing these diseases, of dying of these diseases.

Is it your testimony that over-the-counter diet medications have no value?

Dr. **Wolfe**. My testimony is a little bit different than that. Every drug, assuming that it has some effectiveness, has a benefit and a risk. And when one decides on whether a drug should be on the market in the first instance, when it first is up for approval, or whether it should be removed, you balance the benefits and the risks.

In the case of PPA, the benefits are too small in comparison with the risks, for it to stay on the market, in my judgment, as an over-the-counter drug, and I think you will hear that from a number of other physicians, as well as from victims. I think that the victims who have suffered in ways that they believe are associated with the drug——

Mr. **Lantos**. Could I stop you there?

Dr. **Wolfe**. Yes. They have as much right to speak out as I do.

Mr. **Lantos**. Well, everybody has the right to speak out in a free society. The question I have, which as a logician disturbs me, is that we have testimony of cerebral hemmorrhage, of strokes, and every one of these instances is a tragic human episode. My question is are there studies indicating that you are aware of, that, for instance, strokes occur more frequently in that segment of the population that takes diet pills than in the segment of the population that doesn't take diet pills?

Dr. **Wolfe**. There has not been that large kind of prospective epidemiological study. I'll tell you, Congressman Lantos, the thing that concerns me the most was the study I mentioned briefly before——

Mr. **Lantos**. But could I just——

Dr. **Wolfe**. Wait. I'm answering your question.

Mr. **Lantos**. Please go ahead.

Dr. **Wolfe** [continuing]. The study in perfectly normal people, medical students, as I said, if medical students can be deemed as normal. They did not have any high blood pressure. And when they took amounts of this drug that are pretty much in the same range that we're talking about, a number of them had dangerously high elevations of blood pressure after just one pill. If this were to happen in an older person, I could well imagine that might be one mechanism whereby they would have a stroke.

So, if you take a very well-controlled study on normal people and combine it with a series of anecdotes, as you call them, in which people very shortly after taking one or more of these pills, have a stroke or something else, the evidence begins to mount.

Whether or not we're going to have the perfect study that you are suggesting would be nice to have, and I would agree, is a different question, and whether or not we should wait that long and have more and more anecdotes and more and more strokes until then, is another question. It's an ethical as well as a public health question.

The reason more and more people are suggesting let's get this stuff off the market as an over-the-counter weight reduction pill is that they think that even though the evidence isn't perfect, it's enough to take some action.

Mr. LANTOS. You see, the difficulty with the anecdotal evidence to a layman such as Mrs. O'Reilly or myself, who are not trained in the realm of medicine, but in other fields, at least I have difficulty with this, in that I could visualize a panel of four individuals with equal sincerity relating to us how, having been obese, they had a great deal of difficulty in their personal, social, economic lives, as is obviously the case in American society, and by the successful results that they obtained, through taking these over-the-counter medications, as prescribed, they are now psychologically, socially, economically and every other way functioning in a much more happy, satisfying, fashion.

Therefore, the anecdotal evidence, although it evokes empathy and certainly sympathy in many instances, as far as this Member is concerned, is of no relevance with respect to the issue of devising public policy.

Dr. WOLFE. You're talking about the anecdotes that people say they feel better because they have lost weight?

Mr. LANTOS. No, I'm not talking about——

Dr. WOLFE. Those are anecdotes that are all right, is that what you're saying? There are two kinds of anecdotes?

Mr. LANTOS. No, I am not suggesting that. And I am surprised that that was your interpretation of what I am suggesting. All I am suggesting is that anecdotal evidence, pro or con, is interesting and worthwhile insofar as that relates to specific individuals.

What we are dealing with is a substance which is taken by millions and millions and millions of Americans on a regular basis. I do wish to go back to Contac, because never having taken a diet pill, I can't have anecdotal experience to relate to you. But I can with respect to Contac. It is probably my failure to read the label carefully, but I can't tell you what manufacturer manufactures Contac. I don't know.

What I do know is that it has been very effective. It has been very effective and it contains PPA and I, as a citizen, would be deeply resentful of the FDA were it to remove it from the counter, from the Safeway grocery store counter, where I buy my Contac as I need it, because I believe that I and millions of others, having a bad cold, can make an intelligent judgment as to whether we wish to take them or whether we don't wish to take them.

Dr. WOLFE. Who recommended removing Contac from the marketplace? I did not recommend removing Contac. Did you think that I did?

Mr. LANTOS. But it contains PPA.

Dr. WOLFE. Yes, but the recommendation was, as I guess I didn't make clear that when you look at a product you balance the benefits versus the risks. When you're looking at PPA in diet pills, I believe, and many others do, that the risks overbalance the benefits, and it is in that specific sense that we are recommending that it should not be allowed.

Mr. LANTOS. Yes, but——

Dr. WOLFE. You're raising a different kind of issue.

Mr. **Lantos**. No, I'm raising an identical issue, and the issue that I am raising is that there are millions of people who voluntarily take these, purchase these pills, take them, and presumably find sufficient benefits from them that they keep buying them, they keep telling their friends to buy them. Otherwise there would not be 10 million or whatever the figure is, people who take them.

Dr. **Wolfe**. Well, let me just respond to that. The so-called marketplace test which you're raising, and which many others raise, particularly people in the drug industry, is not valid for a number of reasons. One, many products contain more than one ingredient and it's possible that one ingredient is what is working and the additional one isn't. That's why, as I mentioned before, most of those products, many of the products on the market now, are illegally in the market as far as we're concerned, because they may have four ingredients. Three may be effective; one may be not. The marketplace would say this works; let's keep using it. But the marketplace would be glad if it got the three instead of the four, possibly for a lower price.

Mr. **Lantos**. I think that's a very valid point. Could I stop you on that?

Dr. **Wolfe**. You can stop me wherever you want.

Mr. **Lantos**. If there are four ingredients and three are effective, and the fourth——

Dr. **Wolfe**. Is not.

Mr. **Lantos**. Is not effective, even dangerous, what is the benefit from the point of view of the manufacturer, of insisting on retaining the fourth, dangerous or ineffective, ingredient?

Dr. **Wolfe**. I think you'd have to ask the manufacturers. My answer would be that one of the reasons we have 300,000 different over-the-counter drug products is that the thing that differentiates most of them from one another is the additional ingredient, lacking evidence of safety and effectiveness. The thing that is unique about Anacin is that Anacin has caffeine in it.

If they had to say, when you saw an Anacin ad, "Anacin is just plain aspirin," do you think that they would sell $60 million, $70 million worth a year? So the answer to your question is that the market fixture of many of these products is based on that additional ingredient and they don't want to let go of them very readily. They will be forced to let go of them when the FDA finally requires these ingredients to be removed from the market because they lack evidence of safety or effectiveness.

So, the answer is that companies know they can keep selling and making money from these products that are "unique," even though the uniqueness is with an ineffective ingredient, and they therefore will do it.

Mr. **Lantos**. Are you suggesting that the use——

Ms. **Oakar**. Excuse me. Would you just excuse me, Mr. Lantos, for 1 second?

We do have to leave this room at 1 o'clock. We have a team of medical experts on behalf of the industry and those who may or may not agree with the industry. I would really like to limit the time now, if we could. I think some of the questions about studies can be addressed to the industry and to others who are medical experts who have done the appropriate studies.

Mr. **Lantos**. That's fine, Madam Chairman.

Ms. **Oakar**. Thank you, Mr. Lantos.

Ms. Ferraro?

Ms. **Ferraro**. Might I suggest, Madam Chair, that perhaps we should observe a 5-minute rule for each of the members during the course of the questions?

Ms. **Oakar**. Right. After you we will.

Ms. **Ferraro**. Well, I'll keep myself down to 5 minutes.

I just wanted to say to Tom that I'm sure Safeway and Contac are delighted by his endorsement today, and I'm going to subject him to another anecdote. When I stopped smoking, about 14 years ago, I put on a pound here and a pound there and a pound everyplace else, and decided I was going to lose 10 pounds and went to take diet pills. And what I did was—it was amazing. I can recall taking them for like 3 days and my heart started beating very fast and I cleaned my house as if I was a commercial for the white tornado. I mean I just went—I couldn't believe. I'd be up very early in the morning and I couldn't sleep at night. And I decided that I didn't want to become a nervous wreck, so I stopped taking them and immediately upon stopping taking them the symptoms stopped. Of course, I didn't lose any weight. But at least I was not a total wreck.

Now, I am a very healthy person. I had never had a problem with shortness of breath or any of those other things that started and stopped with the start and stopping of the diet pill. I don't like those things and I would like to see them off the market. But I just want to question Ms. Phipps.

Had you not been a nurse would you have recognized your symptoms as being dangerous?

Ms. **Phipps**. Probably not.

Ms. **Ferraro**. Had you not gotten medical treatment as quickly as you did, what would have been the result?

Ms. **Phipps**. Possibly a stroke could have happened. It's very hard to say. But probably a stroke.

Ms. **Ferraro**. In any of your cases had you asked for doctor's supervision while you were taking those pills? I know I didn't. So, you know—did you?

Ms. **Phipps**. No, I did not.

Ms. **Ferraro**. Had you, had any of you, had doctor's supervision while you were taking the pills?

Mrs. **Sachs**. No.

Ms. **Ferraro**. No? Had you had—had you been to the doctor just previous to that? You were pregnant, Mrs. Davis, so you had been to the doctor.

Mrs. **Davis**. My baby was already 6 weeks old.

Ms. **Ferraro**. Oh, so it was after the baby. So you had already been back for your checkup and everything else and you were in good shape. Your blood pressure, when the doctor checked you, was not high at that time?

Mrs. **Davis**. No.

Ms. **Ferraro**. At your checkup after the baby?

Mrs. **Davis**. I started taking pills after my baby was 6 months old.

Ms. **Ferraro**. OK.

Mrs. Davis. Six weeks old.

Ms. Ferraro. Six weeks old. But had you gone back to the doctor for your visit after having the baby?

Mrs. Davis. No.

Ms. Ferraro. No; but when you were in the hospital your blood pressure was OK?

Mrs. Davis. Yes.

Ms. Ferraro. So you had not had a problem. So there was no history and it was rather a recent check that you had not gotten high blood pressure before that point. It was one that you feel that was connected with taking the pill.

Let me ask you, Dr. Wolfe, you do not suggest taking every drug off the market that has PPA, do you?

Dr. Wolfe. We haven't made that suggestion. As I said, in this book what we've said is that we think that it's safer and as or more effective, when we're talking about the nasal decongestants, which is the other big category of drugs that have PPA, to take the spray or the drop form. But we have not suggested taking that form of PPA off the market.

We agree that it's a much shorter period of use, a day, two, three, as opposed to months or longer, and therefore the risks are fewer. There have been problems associated with it, but the whole nature of the use is such that the problems, I don't think, are as great as with the diet pills.

Ms. Ferraro. With the diet pills, it seems to me that you would not want to eliminate totally an accessory for appetite control from the market. But it's just the fact that you're concerned about these particular accessories.

Dr. Wolfe. Or their predecessors. Amphetamines are the predecessors.

Ms. Ferraro. Well, the question is how does the FDA get to the point where it can allow—what are they doing wrong in testing, in your view?

Dr. Wolfe. Well, the FDA doesn't do anything wrong in testing because they don't do any testing. What goes wrong is that the tests that are submitted by the companies are often poorly done. One of the reasons why it takes drugs longer to get on the market is that the FDA has to send back to the companies poor quality studies.

In this case I think that a mistake was made by the panel of experts who evaluated the studies, particularly on the safety of these drugs, and to some extent on the effectiveness. And I believe that this hearing is going to provide a reason for reopening those hearings.

Ms. Ferraro. But my point is this: That there's obviously something wrong with the procedure for this to get through and for other, even prescription drugs, to get through.

Dr. Wolfe. The scope of use has increased a lot. I agree with the statement that the FDA has a lot of dedicated civil servants. Most, if not all, of them are. But the problem is that when the decision was made on this ingredient, the use was nowhere near as extensive as it is now and, unfortunately, it has taken that widespread use to collect the amount of information that is now collected. So, I think that they might make a different decision today, and I hope they will.

Ms. **Oakar**. Could I just correct one thing? There is no decision on these drugs.

Dr. **Wolfe**. It's not been—there's no final monograph yet.

Ms. **Oakar**. That's right.

Dr. **Wolfe**. But their tentative decision was to say that it was in category 1, or safe and effective.

Ms. **Ferraro**. Well, it seems to me that the committee should perhaps look at some oversight as far as what the FDA is doing as far as their procedure is concerned. It's not up to us to take a drug off the market. It's put to them, to make sure that it's safe before it's put on the market. Thank you, Madam Chairman.

Ms. **Oakar**. Thank you. And I want to thank the panel, particularly the victims, who came from all over the country to be with us today. It was a hardship to get here. Thank you very, very much. I would also like to submit for the record some letters I have received from other victims of diet pills.

25 Stonegate Road,
Ossining, N.Y., July 22, 1983.

Mr. Daniel Rosenblum,
Staff Assistant,
Congress of the United States,
Washington, D.C.

Dear Mr. Rosenblum: As per my husband's telephone conversation with you, I am submitting a statement which I hope will help you at the hearing.

Sometime in September 1981, I had decided to take Dexatrim to lose weight. I had taken about 5 or 6 pills over a period of 10 days.

One morning I began to have these violent headaches and nausea. I have never had this feeling before. The following day, I went to work when again this feeling came over me. One of my co-workers took me to my doctor. Upon examining me and my telling him what I had taken and the symptoms I had, Dr. Heckman thought it might have been from the Dexatrim. He told me to go home and rest. He would not prescribe any medication, for fear of triggering off another headache. That evening every hour on the hour, I kept having the headaches and nausea.

The following morning, upon awakening I again started with the same headaches. I was sitting in bed and my hands became paralyzed—they were in a locked position, at which time I thought I was having a stroke, or dying. My husband and I became hysterical. He immediately called Dr. Heckman who informed us to go to the hospital where Dr. Weintraub, a neurologist would meet with us. Dr. Weintraub felt after examining me and his past experience with this type of case, my condition was due to the Dexatrim.

I am very sorry that I am unable to appear at the hearing, but I wish you every success in your crusade and if there is anything more I can do, please do not hesitate to call.

Very truly yours,

Lorraine Michaelis.

Bruce H. Heckman, M.D., MPH.,
Ossining, N.Y., July 19, 1983.

Congresswoman Mary Rose Oakar,
2436 Rayburn Building,
Washington, D.C.

Dear Congresswoman Oakar: Mrs. Lorraine Michaelis had the onset of a severe pounding headache on 9/30/81. She was seen by me on 10/1/81 with hot sweats, nausea, vomiting and some diarrhea. She also had some pain in the upper chest. She was given Fiorinal with no real response. The headache became severe again on 10/2/81 and she was seen by a neurologist in emergency consultation, Dr. Michael Weintraub. An electroencephalogram and computerized tomography of the brain were performed and were normal. Slowly the headache dissipated over time.

The feeling of both Dr. Weintraub and myself is that Mrs. Michaelis' headaches were precipitated by taking an over-the-counter "diet pill" containing phenylpropanolamine.

It is my opinion that these medications should be removed from the market since their potential for causing life-threatening illness and abuse far outweigh its long-term beneficial effects in weight loss.

Sincerely,

Bruce H. Heckman, M.D., MPH.

Michael I. Weintraub, M.D., F.A.C.P., P.C.,
Briarcliff Manor, N.Y., July 17, 1983.

Hon. **Mary Rose Oakar**,
Congress of the United States,
House of Representatives,
Washington, D.C.

Dear Representative Oakar: I am sorry that I could not attend your hearings. In my discussion's with Daniel Rosenblum, he indicated that a letter might be of some benefit to you and your committee. Briefly PPA is an active ingredient in diet pills and may be combined with caffeine. Its alleged action is "to help people lose weight" in association with an appropriate diet. This drug has a similar chemical formula to amphetamine, which is "speed" or an "upper." These pills achieve a *high* by their stimulatory effects on both the brain, heart and musculo-skeletal system. Thus, it is not surprising to see some bodily response to this medication, based not only on dosage but also individual sensitivity. In the medical literature headaches, rapid heart rate, arrthymias, palpitations, convulsions, psychosis and death have been reported. Many people, in fact the majority, do not consider this medication when questioned in routine medical examination. They are unaware that these pills may produce bodily changes, rather than the "alleged" weight reduction. Thus it is not uncommon that physicians in practice will encounter patients who are on these pills and who may be symptomatic with some complications, thereof. I have been exposed to several patients who have encountered complications with PPA. As you know I interpreted a CAT scan on Lorraine Michaelis who was sent by her physician for unexplained headaches, to rule out stroke and tumor. This test was normal and I sought to relieve her anxiety about these results. as we spoke she informed me that she was taking dexatrim, etc. and experienced severe headaches, sweating and pupillary dilation. I told her that this was probably secondary to her diet pills, because of the stimulatory structure of the medication. I also informed her that I had other patients who had some neurological symptoms as a result of this medication. I did not formally evaluate Mrs. Michaelis but only performed a CAT scan at the request of her physician.

As I mentioned I know of other complications with PPA induced convulsions. It is not surprising that this "mild" stimulant would achieve a "moderate or severe" stimulating effect on the grain cells which can produce a spectrum of a "high" or jitteriness or convulsions or hallucinations or frank phychosis. Often these drugs produce observable rhythm changes on the electroencephalogram (EEG) and I have seen this. One of my patients, Donata Taylor, who was previously healthy took PPA to achieve weight loss. She had grand mal seizures with EEG changes. I believe that PPA included a stimulating bombardment of irritation to her brain cells that ultimately culminated in her having convulsions. The cells became so overwhelmed, in a susceptible individual, that they released all their energy into a clinical seizure. Many patients show excess beta activity on their EEG while on PPA.

The brain centers for cardiac function can be stimulated by PPA and they produce cardiac irregularities which can culminate in death. Recently we had a teenager who took an overdose of Dexatrim and was admitted to the ICU for this cardiac arrythmia. She almost died.

As you can see there is a broad spectrum of clincal responses that any individual may develop and there is no way to predict who is suspceptible and at what strength of dosage. As with any medication, abuse occurs and consequently withdrawal states can arise when the medication is discontinued.

I feel your committee has an important task and should arrive at a decision requiring a prescription for this drug. I also feel there is a more important overriding issue—do these pills serve any purpose and specifically do they achieve weight loss? To the best of my knowledge there is no medical evidence that statistically demonstrates that these pills work better than placebo, diet, exercise etc. Since overweight status and obesity is a multifactorial phenomena that is chronic, how does a three week trial serve any useful purpose? I strongly feel that your committee recommend that a multi-center short term trial be set up, under government supervision in NIH, with age-matched, psychologically matched, weight-matched controls to determine if these drugs are effective. The results of this study, including complications, will become clearcut and the appropriate decisions can then be made.

The above represents my honest opinions on the matter of PPA. Your reputation for hard work, determination and honesty have my utmost respect.

With best wishes.

MICHAEL I. WEINTRAUB, M.D.,
Clinical Professor.

JOHNSON CREEK, WIS., *May 14, 1982.*

FOOD AND DRUG ADMINISTRATION,
Dockets Management Branch,
Rockville, Md.

DEAR SIRS: Before you make your final decision as to whether or not P.P.A. should be allowed in O.T.C. drugs and medications, I would like to relate what happened to me.

I started taking Dietac to lose weight and followed label directions, taking one time-release capsule a day. (each contained 75 mg. P.P.A. and 200 mg. caffeine.)

On January 19, 1981, I suffered with what was diagnosed as a stroke. Hospitalization and a battery of tests revealed an area of damage to the blood vessels in the right side of my brain. Because I was only 28, healthy and with no history of medical problems, my doctor was puzzled as to the cause.

On October 19, 1981, I heard a report on the radio linking P.P.A. usage with high blood pressure, personality changes and stroke. I got in touch with the Center for Science in the Public Interest, who had released the report. They have been a wealth of information. The more I read, the more convinced I became that my stroke was probably caused by P.P.A. usage.

I know I am not alone. There are many people who have suffered medical problems for no apparent reason, except for using a product containing P.P.A.

I feel that if there is even the slightest bit of doubt concerning the safety of the use of a product, then it should not be allowed in an O.T.C. item. If the F.D.A. is to err in its decision, it would be much to better to err on the side of safety, and not allow P.P.A. to be sold in O.T.C. products.

Sincerely,

FRANK ADAMO.

My name is Donata Taylor and I am eighteen years of age, having been born on February 7, 1965, in Port Chester, New York. At the time I became ill about two years ago from taking diet pills, I lived with my parents, John and Patricia Taylor on Baldwin Place in Mahopac, New York. I was sixteen years of age at the time.

I am 5′2″ tall and two years ago weighed about 140 lbs. I felt I was overweight and wanted to lose weight, so I went to a local drugstore in Mahopac, New York, and looked around on the counters for some sort of pills that would help me lose weight. I picked out the Dexatrim. I chose that brand myself, no one recommended it to me. I followed the directions and began taking these pills according to the directions, one each day. This went on for about one month or one and a half months when I became ill.

I had been home the night before and I believe it was on a weekend in April, 1981. I had a good nights sleep and got up as usual at 7:00 A.M. I suddenly felt tired, really tired, and I went to my room to lay down and go to sleep. This was about 10:00 A.M. I woke up about 2 hours later and began to go downstairs to the kitchen when apparently I had some sort of seizure while going down the stairs. My parents were there and helped me. They called the local ambulance squad and they took me to the Putnam Community Hospital in Carmel, New York, where I stayed for two days. My doctor was a neurologist, Dr. Michael Weintraub, who has offices in Ossining, New York and Carmel, New York. I remember waking up in the hospital. When I came to, I was in a bed in the hospital and while talking to the doctor, I explained to him that I was taking Dexatrim for about a month or more. I was given a variety of tests including an E.E.G. He spoke to my parents more about what had happened to me. The doctor told me that I had had an epileptic seizure and that it was due to the diet pills that I was taking. When I left the hospital after two days, the doctor prescribed medice for me, Dilantin. At first I took only the Dilantin three times a day and I had more seizures at home. Then the doctor added Depocaine and I took that three times a day, also. Since then, I have not had any more seizures.

After I got out of the hospital, I saw the doctor every two months and then every three months and then every six months. He has taken blood tests regularly and I had a Cat Scan and a Spinal Tap. I think they were done about one year after I was released from the hospital.

During the last year I have not had any more seizures but I have to take both medications three times a day. Dr. Weintraub told me that I will have to take the medications for the rest of my life. Early in 1983, I moved from my parents' home to live with my grandmother, Rose Lanza, and still live with here at 370 Westchester, Port Chester, New York 10573. One night we were watching television and we saw that there was a discussion about the effects of diet pills on some people like myself. My older sister, Darlene, had also tried these pills at the time I was on them, but she had no problem with them. My grandmother even tried them but had to stop because she did not feel good, possibly because of her high blood pressure or other problems. By the way, when I was taking Dexatrim, I only lost two pounds.

When I had those other epileptic seizures at home when I first came out of the hospital, they were pretty violent and my two older brothers had to hold me down. I have no memory of those seizures but my parents and my brothers told me about them. Prior to having seizures, I was never seriously ill during my life. While I was taking the Dexatrim, I was on my normal diet. I had previously never been hospitalized or sick except for an occasional cold. I recently saw Dr. Weintraub again and he said I was doing okay but that I should definitely keep taking the same two medications three times a day. I am now out of high school and I work full time as a waitress.

I have signed this statement voluntarily this —— day of July, 1983.

DONATA TAYLOR.

I head a Company with 23 employees. Part of the reason for my stopping to take Dexatrim is that my associates were convinced that the capsules made me "crazy" and impossible to deal with. I myself noticed this effect.

I immediately noticed that taking Dexatrim produced difficulty in urinating. I stopped a day then started again, repeated this several times and was able to confirm the causal connection. First made me think I had prostate problems. I phoned Thompson Medical Co. and spoke to an MD (did not note his name), in order to check this side effect. After a bit of discussion in which he asked me to write them a letter indicating that Dexatrim had helped me to lose weight (that's true), he admitted that the urinating difficulty side effect had indeed been reported previously, but that this was a temporary effect which would cease when I stopped taking Dexatrim, which indeed it did. The same MD explained that the drug contained in Dexatrim has been known for decades as a decongestant whose side effects had been apetite loss, and that Thompson simply turned this around to capitalize on the side effect. I indicated to him that I had not noticed any decongestant qualities, and that I actually need Afrin at times for that purpose. I was not, however, taking Afrin during this period.

STEPHEN F. TEMMER.

Ms. OAKAR. Our next panel includes Charles Nelson, who is the Assistant Chief Postal Inspector, Criminal Investigations, U.S. Postal Services of Washington, accompanied by George Davis, and Ms. Bambi Young, who has probably done the most extensive study in monitoring the diet pill industry. She is with the Center for Science in the Public Interest here in Washington.

We would like to ask you if it's possible to limit your testimony so that we can get to questions. Let's say 10 minutes each so we can really get to all of the panelists, in a spirit of fairness. Mr. Nelson, would you like to proceed?

PANEL 2—CONSUMER ADVOCATES, CONSISTING OF CHARLES P. NELSON, ASSISTANT CHIEF POSTAL INSPECTOR, CRIMINAL INVESTIGATIONS DIVISION, U.S. POSTAL SERVICE, WASHINGTON, D.C., ACCOMPANIED BY GEORGE DAVIS, ASSISTANT GENERAL COUNSEL, CONSUMER PROTECTION DIVISION OF THE LAW DEPARTMENT, U.S. POSTAL SERVICE; AND BAMBI BATTS YOUNG, CENTER FOR SCIENCE IN THE PUBLIC INTEREST, WASHINGTON, D.C.

STATEMENT OF CHARLES P. NELSON

Mr. NELSON. Yes, thank you, Madam Chairman. I have submitted my formal testimony for inclusion in the record, and, with your permission, I'll summarize that testimony at this time.

Ms. OAKAR. Without objection.

Mr. NELSON. We appreciate the opportunity to appear before this subcommittee to discuss the findings of our joint effort to identify problems associated with the sale of diet drugs through the mails, as well as the Postal Service's role in curtailing the sale and distribution of look-alike drugs. As part of a continuing program to protect elderly citizens, a postal inspector, in the fall of 1980, was assigned to work full time with the members of this subcommittee in a joint investigation of mail fraud schemes perpetrated against senior citizens.

One aspect of that investigation focused on the phony weight loss programs and diet pills sold through the mails. We share your concern about the health hazard that stimulants and chemical additives, such as PPA, contained in these products may have on the American public, particularly on the elderly.

As a result of our joint investigation, three diet products were challenged under the false representation statute. H & L Labs, Inc. of Norwalk, Conn., distributed a diet product called "New Quadplan," containing PPA, benzocaine, and other ingredients. Enclosed with the product was a thousand calorie diet labeled "Quadplan Diet Menu Plan." The product was promoted by direct mail advertising during 1980 and 1981.

The advertising claimed it to be "The most powerful reducing aid ever released without a prescription." Prices ranged from $9.95 for a 15-day supply to $38.95 for a 90-day supply. A medical opinion obtained refuted the exaggerated advertising claims for the product.

In September 1981, the firm signed a consent agreement with the Postal Service agreeing to modify its advertising.

Cove Pharmaceutical Sales of Central Islip, N.Y., promoted a diet capsule and a company diet plan called "PPA+Plus," again via direct mail advertising, from September 1980 through August 1981. The advertisement claimed dramatic, permanent, and immediate loss of fat and/or weight. Prices ranged from $5.95 for a 15-day supply to $30 for a 120-day supply. The product contained PPA and caffeine. A medical opinion obtained refuted the claims and stated that this combination is ineffective as an appetite suppressant.

On August 10, 1981, a false representation order was issued against the firm.

A product called "Perma-Loss," distributed by That Special Look, Inc., of Pompano Beach, Fla., contained PPA and caffeine and was accompanied by a sample 4-day diet plan. During 1981, this product, which sold for $9.95 for a 40-day supply and up to $16.95 for a 90-day supply, was advertised in national publications. Exaggerated claims were made such as, "Now you can shed pounds and inches without dieting. You won't even miss snacks or suffer torturous exercises, or subject your body to dangerous drugs."

A medical opinion obtained refuted the product claims as false and misleading.

In September 1981, the firm signed a consent agreement with the Postal Service agreeing to change its advertising.

The next subject we would like to discuss involves a product which is not directed at the elderly, but it still affects all of us as parents and grandparents because it is targeted at our children.

We began our investigation of look-alike drugs in September 1980, after receiving complaints relating to what appeared to be the indiscriminate sale and distribution of controlled substances by mail. Typically, advertisements included full color photographs of the drug products offered for sale and touted the drug's close physical resemblance to genuine controlled substances. The advertisements often claimed the products offered were 100-percent legal and 100-percent safe.

Based on what we believed were material misrepresentations in the advertising for look alikes, administrative actions were initiated against the distributors under title 39, United States Code, section 3005. This section permits the Postal Service, following procedures before an administrative law judge in conformity with the Administrative Procedure Act, to withhold and return to the sender mail addressed to anyone who is engaged in a scheme to obtain money or property through the mails by means of false representations.

Between May 1981 and May 1982, the Postal Service filed 48 complaints alleging violations of title 39, United States Code, section 3005.

In the complaints filed with the administrative law judges, we alleged the principal distributors of these look-alike drugs made the following false representations in their advertisements: One, the drug products involved may safely be used by the general public; two, the drug products involved are prepared, labeled, and marketed in accordance with Federal Food, Drug, and Cosmetic Act requirements; three, the drug products were designed for resale to third persons as controlled substances.

While I believe the Postal Service has diligently pursued its responsibility in this area, I must point out our administrative authority in these investigations is limited to the mail order aspect of these businesses. While initially our efforts curtailed the mail order sales and distribution of these products, many of the major promoters began circumventing the mail stop orders and consent agreements by continuing their activities outside the mails.

Some current advertisements tell prospective customers that only telephone orders will be accepted and that payment must be by credit card, bank wire, or via UPS C.O.D. These procedures avoid the solicitation of money or property through the U.S. mail, thereby avoiding Postal Service jurisdiction under the false representation statute and rendering any preexisting mail stop orders ineffective.

An example of this type of evasive activity practiced by an Ohio-based firm called Brant Pharmacal is shown on the chart now before you.

Many distributors have dropped most of their over-the-counter drugs that resemble genuine drugs of abuse. Many have dropped from their advertising the colored pictures of the items being offered for sale. Most have added cautions against use by persons with particular health problems or conditions and contain specific warnings against resale.

There has been a marked reduction in the kind of advertising cited in our earlier actions. The Postal Inspection Service continues to monitor look alike drug advertising and to investigate companies where advertising appears to be false and misleading or to in violation of the administrative orders and agreements which concluded our cases.

We thank you for the opportunity to appear before this subcommittee and are prepared to answer questions.

[The prepared statement of Mr. Nelson follows:]

PREPARED STATEMENT OF CHARLES P. NELSON, ASSISTANT CHIEF POSTAL INSPECTOR, CRIMINAL INVESTIGATIONS, U.S. POSTAL SERVICE, WASHINGTON, D.C.

Mr. Chairman: My name is Charles P. Nelson, and I am the Assistant Chief Postal Inspector for Criminal Investigations. I appreciate the opportunity to appear before this subcommittee to discuss the findings of our joint effort to identify existing problems associated with the sale of diet drugs through the mails as well as the Postal Service's role in curtailing the sales and distribution of look-alike drugs.

As part of a continuing program to protect elderly citizens, a Postal Inspector in the fall of 1980, was assigned to work full time with members of your staff in a joint investigation of mail fraud schemes perpetrated against senior citizens.

One aspect of that investigation focused on phony weight loss programs and diet pills sold through the mails. We share your concern about the health hazard that stimulants and chemical additives such as phenylpropanolamine (PPA) contained in these products may have on the American public, particularly the elderly.

The Postal Service has been active for many years in attempting to curb false and exaggerated advertising claims relating to the mail order sale of diet products. As a result of our investigations, we have also become aware of the fact that many of the diet products sold by mail contain ingredients which in unregulated doses could be potentially harmful to the elderly, particularly those with medical problems.

We have on many occasions challenged exaggerated mail order claims for "miracle" diet pills containing PPA under the postal false representation statute, 39 U.S.C. § 3005, and products containing PPA have been the subject of prosecution under the criminal mail fraud statute, 18 U.S.C. § 1341.[1] Concern over the possible health risk associated with PPA and the misuse of this drug to obtain a "high" are also familiar. In 1957, representatives of the Post Office Department's General Counsel's Office and the Inspection Service testified before a congressional committee concerning false and misleading advertising of weight reducing aids. In the same hearing, the committee received the testimony of Dr. Leon Hirsh of Cincinnati, Ohio, Dr. Hirsh testified that advertising claims alleging that PPA was a "wonder drug" which permitted loss of weight without caloric restriction were false, Dr. Hirsh also testified that:

> Uncontrolled use of phenyl propanalomine in susceptible individuals could produce temporary elevation of the blood pressure, coronary heart attack, mesenteric thrombosis, cerebral hemorrhage and even death.
>
> The unrestricted sale of such a stimulant as phenyl propanalomine, especially when coupled with caffeine, could have profound deleterious effects.
>
> In our city, one radio station (WSAI) saw fit to promote this combination of drugs in the late afternoon when high school students would be returning home in their

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[1] *U.S.* v. *Andreadis*, 366 F.2d 423 (2nd Cir. 1966).

cars with their radios on. The type of stimulating "jag" produced in young individuals, with drugs of this nature is pretty well known.

I consider the particular product and others similar to it containing phenyl propanalomine potentially dangerous, and not in the public interest and a deteriment to the public health.[2]

In 1978 and 1979, a report was issued to the Food and Drug Administration entitled "Tentative Findings of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products." The report concluded that, under particular conditions, diet products containing PPA were both safe and effective as appetite suppressants. Because the validity of scientific claims is tested in our proceedings against the consensus of informed scientific opinion, we have, since the release of the report, not challenged advertising for diet products in which the claims are consistent with the findings of the advisory review board.

As a result of our joint investigation, three diet products were challenged under the false representation statue:

H & L Labs Incorporated of Norwalk, Connecticut, distributed a diet product called New Qaudplan containing PPA, benzocaine, and other ingredients, enclosed with the product was a thousand-calorie diet labeled "quadplan diet menu plan." The product was promoted by direct mail advertising during November 1980 through September 1981. The advertising claimed it to be "the most powerful reducing aid ever released without a prescription." Prices ranged from $9.95 for a 15-day supply to $38.95 for a 90-day supply, a medical opinion obtained refuted the exaggerated advertising claims for the product. In September 1981, the firm signed a consent agreement with the Postal Service agreeing to modify its advertising.

Cove Pharmacal Sales of Central Islip, New York, promoted a diet capsule and accompaning diet plan called "PPA + Plus" via direct mail advertising from September 1980 through August of 1981. The advertisement claimed dramatic, permanent and immediate losses of fat and/or weight. Prices ranged from $5.95 for a 15-day supply to $30.00 for a 120-day supply. The product contained PPA and caffeine. A medical opinion obtained refuted the claims and stated that this combination is ineffective as an appetite suppressant. On August 10, 1981, a false representation order was issued against the firm.

A product called Perma-Loss distributed by that Special Look, Inc., of Pompano Beach, Florida, contained PPA and caffeine and was accompanied by a sample four-day diet plan. During 1981, this product which sold for $9.95 for a 40-day supply and up to $16.95 for a 90-day supply, was advertised in national publications. Exaggerated claims were made such as "Now you can shed pounds and inches without dieting. . . . You won't even miss snacks, or suffer torturous exercises, or subject your body to dangerous drugs." A medical opinion obtained refuted the product claims as false and misleading. In September 1981, the firm signed a consent agreement with the Postal Service agreeing to change its advertising.

The next subject I would like to discuss involves a product which is not directed at the elderly, but it still affects all of us as parents and grandparents because it is targeted at our children.

We began our investigation of look-alike drugs in September 1980 after receiving complaints relating to what appeared to be the indiscriminate sale and distribution of controlled substances by mail. Typically, advertisements included full-color photographs of the drug products offered for sale and touted the drugs' close physical resemblance to genuine controlled substances. The advertisements often claimed the products offered were "100 percent legal" and "100 percent safe."

Samples of numerous look-alike drugs being distributed by mail were obtained and reviewed by a medical expert. It was determined that they typically contained a combination of caffeine, ephedrine sulfate, and PPA. Over-the-counter diet products containing some of these ingredients, but not in this triple combination, are available without a doctor's prescription in packaging which contains dosage information and warnings restricting use by persons with particular medical conditions.

In a medical opinion provided to the Inspection Service on products containing this triple combination of ingredients, Dr. Sorell L. Schwartz of the Department of Pharmacology, Georgetown University Medical and Dental Schools, stated they should "be considered a recognizable danger to public health." Of these particular ingredients, Dr. Schwartz warned that PPA was notably dangerous since it can cause elevation in blood pressure and exacerbate other cardiovascular disease.

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[2] Hearings before the Subcommittee on Legal and Monetary Affairs of the House Committee on Government Operations concerning *false and misleading advertising of weight reducing aids,* August 7, 1957, pp. 123-124. See also House Report No. 2553, 85th Congress, 2nd session, August 12, 1958.

Based on what we believed were material misrepresentations in the advertising for look-alikes, administrative actions were initiated against the distributors under title 39, U.S. Code, section 3005. Section 3005 permits the Postal Service, following procedures before an administrative law judge in conformity with the Administrative Procedure Act (5 U.S.C. Chs. 5, 7) to withhold and return to the sender mail addressed to anyone who is engaged in a scheme to obtain money or property through the mails by means of false representations. Between May 1981 and May 1982, the Postal Service filed 48 complaints alleging violations of title 39, U.S. Code, section 3005.

In the complaints filed with the administrative law judges, we alleged that the principal distributors of these look-alike drugs made the following false representations in their advertisements.

1. The drug products involved may be safely used by the general population.

2. The drug products involved are prepared, labeled, and marketed in accordance with the Federal Food, Drug and Cosmetic Act.

3. The drug products were designed for resale to third persons as controlled substances.

A basic premise of the cases was the contention that the offered drug products resembled and were easily mistaken for other illegally trafficked drugs containing controlled substances. By language, pricing and other means, the promoters encouraged resale of the drugs by their customers to others. Thus, we believed the sellers were providing their customers, and encouraging them to use, the means to deceive others concerning the actual content of these drugs. The advertisements used street jargon to describe their products such as "blue and clear," "brown and clear," "robin eggs," "714's," "black beauties," and "yellow jackets."

Our evidence showed that those purchasing look-alikes—both directly from promoters and street corner "pushers"—were junior high, high school, and college-age young people. Of particular concern was evidence of trafficking and use by elementary school children.

The 48 administrative complaints we have filed related to look-alike drug distributors located throughout the country. While I believe the postal service has diligently pursued its responsibility in this area, I must point out our administrative authority in these investigations is limited to the mail order aspects of these business. While initially our efforts curtailed the mail order sale and distribution of these products, many of the major promoters began circumventing the mail stop orders and consent agreements by continuing their activities outside the mails. Some current advertisements tell prospective customers that only telephone orders will be accepted and that payment must be by credit card, bank wire, or United Parcel Service C.O.D. These procedures avoid the solicitation of money or property through the U.S. mail, thereby avoiding Postal Service jurisdiction under the false representation statute and rendering any preexisting mail stop orders ineffective.

An example of this type of evasive activity practiced by an Ohio based firm called Brant Pharmacal is shown on the chart now before you.

Many distributors have now dropped most of their over-the-counter drugs that resemble genuine drugs of abuse. Many have dropped from their advertising the colored pictures of the items being offered for sale. Most have added cautions against use by persons with particular health problems or conditions and contain specific warnings against resale. There has been a marked reduction in the kinds of advertising cited in our earlier actions. In fact, I understand that the street term for these drugs is changing from "look-alikes" to "act-alikes."

In retrospect, our actions against mail order distribution of look-alikes may prove to have been a useful holding action. Our efforts hopefully gave Federal and State drug enforcement agencies and legislative bodies time to initiate legal actions and enact legislation which could have a more permanent effect upon the abusive distribution of these drugs.

However, the Postal Inspection Service continues to monitor look-alike advertising and to investigate companies whose advertising appears to be false and misleading or to be in violation of the administrative orders and agreements which concluded our cases.

Thank you for the opportunity to appear before this subcommittee. I would be happy to answer any questions.

Ms. **Oakar**. Thank you, Mr. Nelson.

Ms. Young?

STATEMENT OF BAMBI BATTS YOUNG

Dr. YOUNG. My name is Bambi Batts Young. I hold a doctorate in biochemistry and I'm director of the environment and behavior program at the Center for Science in the Public Interest. The center is a nonprofit consumer organization with about 30,000 members who are strongly committed to improving national dietary and health policies.

The center is joined in its testimony today by the National Women's Health Network, which is the largest women's health organization in the United States.

Congresswoman Oakar, members of the subcommittee, we very much appreciate the opportunity today to voice our concerns about over-the-counter products, diet products, that contain PPA. Now, these products are unsafe for many of the people who take them, at any age, but certainly the greatest burden of risk would fall upon the elderly.

We are therefore pleased that the committee, subcommittee, has taken the lead in bringing this problem up for a full and public hearing.

Our interest in this drug dates back to 1981 when a review of the medical literature and of FDA files convinced us that PPA-based pills are potentially dangerous for two reasons. First, they have a tendency to raise blood pressure in a substantial number of the people who use them. Second, they do have some stimulant properties that have led to widespread abuse problems among young people and may contribute, as well, to discomfort and behavioral problems even among people who take them as recommended.

We also noted in 1981 that advertising for the over-the-counter diet pills containing PPA was grossly misleading, using tactics that had been ruled unacceptable by the Federal Trade Commission and the courts during the 1970's.

Accordingly, in the fall of 1981, the Center for Science filed a—what's going on?

Ms. OAKAR. Well, we might be having some votes but it's all right. Just go ahead. Keep going on.

Dr. YOUNG. Well, that's important.

Ms. OAKAR. No, we don't think it's a vote, so just continue.

Dr. YOUNG. In the fall of 1981 the center filed a petition with the Federal Trade Commission asking for action against the misleading advertisements. In addition, we then wrote to Commissioner Hayes of the Food and Drug Administration urging the agency to conduct an accelerated review of these products with an eye toward banning them from the over-the-counter market.

Since that time, we have continued to press both agencies for better regulatory controls over PPA-based diet pills. This spring the Federal Trade Commission issued an extremely limited warning about the deceptive ads. The FDA says it's still reviewing the data.

We too have reviewed all the safety and effectiveness data that have been submitted to agencies by either the diet pill manufacturers or other interested parties. The more we've seen, the greater our concern has grown.

Our concern rises from several sources. For one thing, we have seen a growing number of people, like the witnesses that you saw earlier, who report that they've experienced severe, sometimes life-threatening, attacks following the ingestion of either a single or, at most, a double dose of PPA-normal use, not abuse.

You've seen some of them. Others are reported in the medical literature. Close to two dozen cases of serious damage have been registered with our hazard clearinghouse for PPA diet pills, as well as hundreds of reports of milder, but still distressing, symptoms, and the Food and Drug Administration in its adverse reaction reports also includes some examples.

There's a common strain of symptoms that runs through all of these reports, which is what you might expect if you had a drug that stimulated the heart and the brain. What comes up time after time is a racing feeling, a severe headache, blood pressure rises, and, in extreme cases, stroke, seizures, and mental disturbances.

Now, I know we've heard that these are just anecdotes, they're stories, and in fact, you can't prove that the damage these people suffered was caused by the PPA. That's true in many human health hazards. There's no clear proof. But I would caution you to remember that that's precisely what was said a few years back about the thalidimide babies, and it was said for several years. Nevertheless, the defects suffered by those babies were very real, very tragic, and as we later found out, very much due to thalidimide. You can't just ignore these people, particularly when their symptoms fit with the scientific evidence, and they do.

However, the human stories don't stand alone. They simply serve to back up the weight of the scientific evidence that has been accumulating over the past few years.

One way to look at the evidence is to ask what is the drug's structure; what other drugs is it related to: what do they do?

Phenylpropanolamine is almost identical to amphetamines in structure. It's in the same chemical family. It is not as strong. I don't want to imply that. It is a weaker cousin of amphetamine. The chemical class that it fits in has general properties of raising the heart rate, speeding it up, altering muscle tone in the blood vessels, and stimulating the brain.

The medical community generally recognizes that though PPA is weaker, it does share in many of these properties and, therefore, it recommendes that people who have such disorders as hypertension, heart disease, diabetes, or thyroid disease, should not take PPA at all, or if they do so, should do it only under the supervision of a physician.

The question then rises, how many of the people who are likely to take diet pills suffer from one or more of those conditions? The answer is: Probably most of them.

Let's just look at the people who have hypertension. In the American Adult population at large, you have a 20-percent hypertension rate. But people who are overweight have a far greater probability of developing hypertension—to the tune of 1½ to 4 times greater.

That means, if you do the calculations, that roughly a third of the overweight people generally have definite hypertension. Many more probably have borderline hypertension or one of the other disorders for which PAA is contraindicated.

Bad though the situation is for the general overweight population, it becomes far worse as people age. Hypertension rates go up with years not just weight. And the combination of age and weight is extremely grim. The Government-sponsored Framingham study found that 46 to 47 percent of overweight men and women who were studied between the time they were 50 and the time they reached 59, had definite hypertension, not even borderline.

The rising frequency of diabetes with age is also extremely alarming. One national survey indicates that the heaviest people between the ages of 45 and 64 are about 3 to 8 times more likely to have adult onset diabetes than similarly overweight young people and 10 to 20 times more likely than young adults who are of average weight.

All of this adds up to an enormous risk to any dieter about 50 or older. And basically those people simply would be best advised to stay away from PPA diet products. That is what any general medical consensus would say. The elderly are just at too great a risk because of their susceptibility to hypertension and other disorders.

Considering how commonly hypertension and diabetes go along with excess weight, we find it interesting and disturbing that when the manufacturers conduct studies to test the safety of PPA they almost always carefully exclude anyone who has one of those disorders or any other significant health problem. In other words, they carefully exclude most of the people who would be likely to take the pills in real life.

What's even more interesting is that even when you start out with a group that is young, that is exceedingly healthy, and that is of normal weight, some of that group still develops alarmingly high blood pressure in response to a single PPA dose.

Curiously enough, one of the best places to find that evidence is in an industry-sponsored study that has been widely promoted as proof of PPA safety. The study, conducted by a research team affiliated with Johns Hopkins University, and I believe there's a representative of that study here today, gave each of 59 young adults a disguised PPA pill on one day and a dummy pill that looked identical on another day. So nobody could know or expect or get worried about which was which.

Then, in each case, the researchers measured blood pressure at a half an hour, 1 hour, 2, 4, 6, 8, 10, and 12 hours—very careful intervals—after the pill was taken, to see what happened to the blood pressure.

Unaccountably, after taking all these careful measurements all the way along, they lumped all of the figures for the drug day together and all of the figures from the dummy pill data together and they looked and they didn't see much difference and they said, "No problem."

The reported result, as publicized by the diet aid industry is "PPA does not affect blood pressure." I am quoting from a letter that was written to Dr. Novitch at the FDA. Despite those assurances, when we plot out the figures, we see quite a different conclusion.

Ms. OAKAR. Are we getting close to wrapping it up? Because it's getting a little long.

Dr. YOUNG. It won't take too long. I just want to show some curves. Thank you.

There is a clear peak on drug day compared to days of dummy pills. Now, that's only about eight points. You say that's not so big. But that's on the average. If the average increases eight points there are some people who go up a whole lot more, and that's what happens. This is a young man who was 26 years old. His diastolic blood pressure—that's the lower number in the blood pressure reading—went up by 36 points in response to the drug, 36 points.

Another young woman, a 23-year-old woman, started out with a very low blood pressure, around a 90 over 60, but went up to 146 over 90 when she was taking the drug. That's about a 55-point increase in the top number—systolic pressure—and about a 30-some increase in the botton number—diastolic pressure.

All in all, in this study, eight of the individuals had increases that took them into the definite hypertensive range. These are people who started out with blood pressure that is so low that it isn't even representative of the American population at large, much less the elderly.

Ms. OAKAR. You're talking about this Johns Hopkins study?

Dr. YOUNG. That's what I'm talking about.

Ms. OAKAR. It's not your study; it's another study, their study.

Dr. YOUNG. It's the Hopkins study. What I'm saying is if you average everybody together you may not see much, but if you look for individual differences you find that 10 percent of that Hopkins population experienced extremely alarming increases in blood pressure, specifically when they were given the drug, not when they got the dummy. And this was starting out with a population of extremely healthy young people with very low blood pressure.

The same thing was seen in the Australian study that Dr. Wolfe referred to earlier.

Now, I think it's rather difficult to imagine any responsible physician taking a patient who already has hypertension, which these people did not, and recommending that that patient take a nonessential drug, which has been repeatedly demonstrated to cause a spurt in diastolic pressure of 20 or 30 points. It would be considered just not responsible.

Yet, most of the people who take these pills are either hypertensive or borderline hypertensive.

Ms. OAKAR. Bambi, we're going to have to have you respond to questions. We're really just running out of time.

Mr. Lantos?

Mr. LANTOS. I have no questions, Madam Chairman.

Ms. OAKAR. Ms. Ferraro?

Ms. FERRARO. I have no questions.

Ms. OAKAR. Mr. Wortley?

Mr. WORTLEY. I'll pass.

Ms. OAKAR. OK.

Dr. YOUNG. Mr. Wortley, I can respond to that study about the effectiveness, if you're interested. There were three parts to that study, as I recollect. Only one of them was controlled for the effect of dummy medication. The other two cannot be considered adequate scientifically. There was one that did have a dummy pill in there.

The power of suggestion is enormously powerful in weight loss and you've got to have a comparison between the drug and a dummy.

I believe in the case where there was a dummy that the average weight loss was about a third of a pound a week more when you took the drug than when you took the dummy pill, a third of a pound over 6 weeks. Do you really think that the average consumer, if informed, that he or she might lose a third of a pound a week for 6 weeks, would consider that effective?

Mr. WORTLEY. If you're asking me, I'd say no.

Dr. YOUNG. Right.

Ms. OAKAR. Ms. Ferraro, you have one?

Ms. FERRARO. I do just have one question of Mr. Nelson and that was on the charts that you had up here. Unfortunately, I couldn't see them. They're a little bit too far away. You were talking about look alikes.

Mr. NELSON. Yes, that's right.

Ms. FERRARO. What are they being sold as, cheaper than the brand labels? Are they sold as generics? Is that what it is?

Mr. NELSON. Well, I think they're being sold as an impersonation of the true controlled substance, of abuse-potential drugs that are schedule I controlled substances. They are designed to look just like the hard drugs that you would get. That's why they call them look alikes.

Ms. FERRARO. Oh. But they are not controlled substances?

Mr. NELSON. That's right.

Ms. FERRARO. That's a good news and a bad news type of thing. Thank God they're not controlled substances going to the kids, but by the same token, the kids think that they're getting controlled substances. Is that it?

Mr. NELSON. That's true.

Ms. FERRARO. How do we go after those people who are cleverly using the credit card and the parcel post and all that stuff instead of the mails?

Mr. NELSON. UPS?

Ms. FERRARO. Yes.

Mr. NELSON. There's no way the Postal Service can go after them, as such. It would have to be some other agency, I suppose the FBI or FDA, maybe FTC.

Ms. FERRARO. That's interesting. Thank you. I'd like to see those charts up a little closer, if I might, while the other people are asking questions.

Ms. OAKAR. Thank you, Congresswoman.

Yes, Mr. Wortley?

Mr. WORTLEY. Madam Chairman, just to set the record straight, I think Dr. Young was referring to something else. It's apparently not the same study that I was working from. In this study it says that in each of the three studies patients were randomly assigned to groups which were essentially homogenous in terms of entrance criteria. Each experimental group received either a placebo or PPA.

I think we're talking about two different studies.

Dr. **Young**. It's possible, although my understanding was that there were two studies which involved a comparison of PPA with a prescription anorectic, rather than with placebo.

Ms. **Oakar**. Mr. Bilirakis?

Mr. **Bilirakis**. Madam Chairman, thank you. I have problems with that name too, ma'am. Just one quick question. How great is this a problem among the aging? That's this committee's concern. How great is it a problem among the aging?

Dr. **Young**. That's how hypertension goes up when you get older. Hypertension is an enormously important problem for the elderly, particularly. And the point is that it's silent. If you have hypertension you don't necessarily know that you have it. It doesn't have any symptoms. And yet it is the major cause of stroke, new cardiovascular diseases of all sorts in older people.

Mr. **Bilirakis**. Yes, I thank you. I appreciate that. But what I wonder is how many of the aged are using these diet pills, for instance, and these drugs that contain PPA?

Dr. **Young**. Well, the best figure—I mean, I think the best person to ask here is Dr. Charles Winick, who is somewhere in the audience.

Mr. **Bilirakis**. Yes. Did he have to leave?

Dr. **Young**. Well, no, he hasn't given his presentation yet.

Mr. **Bilirakis**. OK.

Dr. **Young**. I do know that in a presentation he gave to the FDA in 1977, it was reported that about a quarter of the users were either under 17 or over 49. People under 17 aren't supposed to take PPA-diet pills at all, according to the package labels. And people over 49 are at great risk.

Since there are 10 million people total taking these things, a quarter of that is 2½ million people. That is not a minor number of people.

Ms. **Oakar**. Could I respond to that point?

Mr. **Bilirakis**. I'll defer, yes.

Ms. **Oakar**. Of the 10,000 individuals in 1 year who have notified the poison center, which is under the auspices of FDA, what you're referring to, Geri, what is their monitoring, three-fourths of them were over 50. In addition, they had 1,000 individual emergency cases, and that's their estimate annually across the country.

In addition to that, I have already submitted this for the record. There are over 1,000 individuals who have reported problems with PPA prescription diet pills and a third of them are over 55. So, it is a problem that cuts across age barriers. But it certainly concerns older Americans.

I just have one quick question and one point to make. In your testimony, Mr. Nelson, you were talking about the mail, which is your jurisdiction. Probably we haven't given the Post Office as much authority as you'd like. But nonetheless, I noticed in the chart that one of the ads was a legal stimulant. Committee staff pointed out to me that the same ingredients in most of the drugs that you have shown in your study, that you have submitted to the staff and our committee some time ago, are the same ingredients as the over-the-counter drugs.

In addition to this, the State of California's attorney general went after one of the manufacturers of diet products. I'm not interested in belaboring whose name it is, unless somebody wants to ask me, because I personally feel that it's a problem with all brands. But they settled out of court because they were using the phrase, "no stimulant," and they were asked to remove that. They settled, then, with the State of California for thousands and thousands of dollars for false advertising. So there's a problem, obviously, through the mail and otherwise.

[Material submitted by Representative Oakar follows:]

THOMPSON MEDICAL COMPANY, INC.
919 THIRD AVENUE • NEW YORK, N.Y. 10022 • (212) 688-4420

February 10, 1983

FEB 1
CONSUMER
FRAUD

Richard Brungard
Deputy District Attorney
County of Ventura
State of California
Hall of Justice
800 South Victoria Avenue
Ventura, CALIF. 93009

Re: Letter Agreement Between Thompson Medical Company and the Ventura County District Attorney's Office

Dear Mr. Brungard:

You and I have discussed Thompson Medical Company's advertising of weight control products extensively, and have reached certain agreements which this letter will memorialize.

With regard to all products manufactured, sold or advertised by Thompson Medical Company for appetite control which contain phenylpropanolamine hydrochloride, our company has agreed henceforth to voluntarily:

1. Make no reference to the safety of the drug in its print advertising unless a statement like the following is given "Before starting this or any diet, consult your physician if you have any underlying health condition such as heart disease or hypertension."

2. Make no reference to the drug being approved by a United States Government advisory panel, or similar language, in any print advertising or packaging until a new monograph is published or released. (This restriction refers specifically to the monograph recommended by the Advisory Review Panel on OTC Miscellaneous Internal Drug Products published in the Federal Register, volume 37, number 39, Friday, February 26,1982).

3. Make no reference to the drug containing "no stimulants" in advertising or packaging.

Thompson Medical Company agrees to begin immediately to implement and abide by the advertising and labeling requirements set forth in the Final Judgment Pursuant to Stipulation, and this Letter of Agreement. With respect to labeling modification, Thompson Medical Company anticipates it may require several months to exhaust current inventory of packaging. All packaging sent to the State of California will comply with these agreements within four (4) months.

This Letter of Agreement can be modified by written agreement between Thompson Medical Company and the Ventura County District Attorney's Office. If no agreement can be reached, the dispute shall be resolved by an arbitrator agreed on by both parties. If no arbitrator can be agreed upon within thirty (30) days of written request, then the Presiding Judge of the Superior Court of Ventura County shall appoint an arbitrator to resolve the dispute.

This Letter of Agreement shall remain in effect for a period of three years.

Please signify your approval of these agreements by signing a copy of this letter at the place indicated below and returning copy to me.

It has been, indeed, a pleasure meeting with you and I personally wish you the best. I sincerely appreciate the insights you shared with us.

Very truly yours,

THOMPSON MEDICAL COMPANY, INC.

SDA:fj

S. Daniel Abraham
Chairman of the Board

AGREED

Richard Brungard
Richard Brungard

Ms. **Oakar.** Bambi, I want to thank you for the fine work that you and the Women's Center have done in this area. It's a thankless job. I know you've run up against all kinds of brick walls and harassments and everything else. But I think the work you're doing is just tremendous and thank you both very, very much.

Our next panel is Dr. Sorrel Schwartz with the department of pharmacology, Georgetown University School of Medicine, Dr. James Ramey, private practive of endocrinology and metabolism, Dr. Thaddeus Prout, associate professor of medicine at Johns Hopkins and chief of medicine at Greater Baltimore Medical Center, and Dr. Shirley Mueller, who is the director of neurology, Reganstreif Health Center, Indiana University School of Medicine, Indianapolis, Ind.

We want to thank you all for coming. We know you're recognized in your field and well published, and thank you so much for being here.

Dr. Schwartz, could we begin with you. Can you make your remarks somewhat brief so that we can get to questions?

PANEL 3—MEDICAL EXPERTS, CONSISTING OF DR. SORELL SCHWARTZ, PROFESSOR OF PHARMACOLOGY, GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE, WASHINGTON, D.C.; DR. SHIRLEY MUELLER, DIRECTOR OF NEUROLOGY, REGANSTREIF HEALTH CENTER, INDIANA UNIVERSITY SCHOOL OF MEDICINE, INDIANAPOLIS, IND.; DR THADDEUS PROUT, ASSOCIATE PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, AND CHIEF OF MEDICINE, GREATER BALTIMORE MEDICAL CENTER, BALTIMORE, MD.; AND DR. JAMES RAMEY, ASSOCIATE CLINICAL PROFESSOR AT GEORGE WASHINGTON UNIVERSITY

STATEMENT OF DR. SORELL SCHWARTZ

Dr. **Schwartz.** Thank you, Madam Chairman.

My comments have been submitted in writing to staff. I would submit them for the record, and in the interest of time, forego repeating them. I would just like to highlight two or three points.

Ms. **Oakar.** Without objection.

Dr. **Schwartz.** The first is that one of the most important aspects of evaluating the safety and efficacy of a drug are the pharmacokinetics. This is determining the absorption, distribution, and elimination of a drug. Toxicologically this is important from the viewpoint of possible accumulation of the drug in the body.

Today there are no standard procedures recommended for animal studies or otherwise by the Food and Drug Administration which require that pharmacokinetic studies associated with age be performed. This is extremely important because we know that the elderly adult has changes in renal function, in liver function, in the volume of water in the body, in the amount of fat in the body, that all impact upon this.

I would also like to point out that the difference between an efficacious over-the-counter drug and a prescription drug is in the therapeutic range. That is, the difference between the effective dose and the toxic dose.

With the over-the-counter drug, the therapeutic range is wide so that there is a leeway for patient error when taking the drug without medical supervision.

We cannot be assured, nor is there any reason to believe, that the therapeutic ranges established for younger and middle aged adults apply to the elderly. So, the safety of over-the-counter drugs in the elderly adult based on our clinical experience in the younger population is not particularly assured.

Those are the points which I would like to highlight from the viewpoint of where I think there might be regulatory needs, or certainly encouraging of regulatory needs. I will say in passing that I worked with the Postal Service on this matter, found the Postal Service to be extremely dedicated. That was fortunate because we also found a great deal of difficulty early on in getting any cooperation at all from the Food and Drug Administration.

Thank you.

[The prepared statement of Dr. Schwartz follows:]

PREPARED STATEMENT OF SORELL L. SCHWARTZ, PH. D., PROFESSOR OF PHARMACOLOGY, GEORGETOWN UNIVERSITY SCHOOL OF MEDICINE, AND SCIENTIFIC DIRECTOR OF THE CENTER FOR ENVIRONMENTAL HEALTH AND HUMAN TOXICOLOGY

Mr. Chairman, my name is Sorell L. Schwartz. I am Professor of Pharmacology at Georgetown University School of Medicine and Scientific Director of the Center for Environmental Health and Human Toxicology. I hold a Ph. D. in Pharmacology from the Medical College of Virginia, Virgina Commonwealth University. Since receiving the degree in 1963, my area of concentration has been primarily in toxicology. A copy of a Curriculum Vitae detailing my educational, research, and other professional background is appended.

It is my understanding that staff wishes me to discuss the matter of advertising and distribution of over-the-counter drugs to the elderly through the mails, in general, and the situation with phenylpropanolamine, in particular. This shall be my task, but I first wish to establish the basis for discussion by introducing a much broader problem. That is the lack of any appreciable information on the toxicity of drugs in the elderly. It represents an alarming gap in our knowledge and, for that matter, in our research efforts.

The evaluation of any new drug begins with animal studies. These studies include the evaluation of the acute toxicity, subchronic, and chronic toxicity of drugs. They involve an evaluation of the pharmacokinetics which gives valuable information on how the drug is absorbed, how it is distributed, and how it is eliminated. Such information is necessary to determine whether accumulation of the drug within the body over a particular dosage schedule is likely to occur or not. Following animal studies, studies are done in normal adult volunteers to determine tolerance levels and, again, to determine pharmacokinetics. These are the so-called Phase I clinical studies. Subsequent to this, clinical studies are then done to evaluate the actual efficacy of the drug. These data are then used to arrive at recommended dosage regimens and warnings for the use of the drugs. To my knowledge, this evaluation procedure rarely, if ever, takes into account the problems of the elderly. This is in spite of the fact that changes in kidney function, liver function, and other factors which influence the ability of the body to handle the drug are known to be different in the elderly when compared to young and middle-aged adults. This is in spite of the fact that the sensitivities of the various physiological systems, e.g., the central nervous system, are known to be altered in the elderly when compared to young and middle-aged adults. This is in spite of the fact that the immune system, the blood-forming tissue, and other physiologic systems which can respond to give serious and life-threatening drug reactions are also known to be acted upon by drugs in the elderly in a manner different in young and middle-aged adults.

One response may be that the Food and Drug Administration requires chronic toxicity studies of drugs to begin at or before birth and to proceed to death of the animal from old age. Without going into the specific reasons, the way in which these studies are done are inadequate to provide us particular information on the effects of drugs in the elderly. An entire new set of protocols is required before we can even begin to predict possible responses in the elderly human from animal studies. I am not suggesting that the elderly become key subjects for Phase I clinical studies. On the other hand, drug labeling requirements addressed to the needs of the elderly involving various precautions in use of drugs are rare. Untoward responses to drugs by the elderly are everyday occurrences . Yet they continue to be referred to as idiosyncratic responses. The commonness of their occurrence belie the use of the word idiosyncrasy.

The fact that polypharmacy (multiple drug therapy) is the rule with the elderly compounds this problem in geometric proportions. Considering the ill-defined nature of drug action in elderly adults along with the dose compliance problems associated with polypharmacy, only an incurable optimist or a fool would expect an uneventful course of pharmacotherapy in an elderly individual. Similarly, over-the-counter drugs which have any efficacy cannot be considered to be toxicologically innocuous. What distinguishes the efficacious over-the-counter drug from a drug requiring a prescription is the dosage latitude between therapeutic efficacy and untoward side effects. Yet, even this assumption cannot be assured in the elderly, especially if that elderly individual is taking prescription drugs in addition to the over-the-counter medication.

This should provide a particular prospective with respect to the use of over-the-counter drugs by the elderly and the encouragement of that use by the mails or any other advertising techniques. This is of concern both with respect to encouraging the elderly to increase the number of medications they are taking, and thereby increasing the compliance problems associated with polypharmacy and with respect to increasing the possibility of drug reaction or interaction with other drugs. The necessity for the risk benefit evaluation is obvious. In many cases, the needs for the potential benefit outweigh the risks. Such is not the case with phenylpropanolamine (PPA).

PPA is a drug which is chemically related to amphetamine. Amphetamine is known for its ability to stimulate the central nervous system, as an appetite suppressant and for its ability to increase blood pressure. The means by which the amphetamine exerts its effect on blood pressure is to constrict blood vessels. Early studies with PPA suggested that it had little of the effects of amphetamine and that its major activity is to constrict small blood vessels. Since the small blood vessels in the nasal tissues are dilated during nasal congestion, PPA, because it can constrict these small blood vessels, was used as a nasal decongestant when taken orally. It now appears that PPA has a much greater likelihood of affecting blood pressure than originally believed. As early as 1965 and 1966 there were reports of incidents of transient hypertension following PPA ingestion [1,2]. A series of reports from Australia from 1978 through 1980 [3-7] focused on the problem of PPA-associated hypertension. One report [7] describes studies of the effects of either 50 mg. or 85 mg. of PPA in medical students. The high dose caused an increase in blood pressure diagnostically classified as a hypertensive response in 12 of 37 subjects. Hypertensive reponses to PPA have now been documented on numerous occasions in this country and other counties [6, 8].

The elderly are susceptible to changes in blood pressure, both those that can result in a reflex hypotensive response and resultant fainting and injury during fall as well as a cerebrovascular accident from the hypertension. Work done by the Center for Forensic and Environmental Science at the University of New Mexico School of Medicine has revealed three deaths associated with intracranial hemorrhage from the ingestion of look-alike drugs by young people. Though the implication of look-alike drugs is that there was an abuse involved, this is not entirely certain; and the idea that PPA could cause a stroke in a young person leads to some frightening concerns about the elderly vis-a-vis the discussion above regarding differences in physiologic sensitivities.

PPA is marketed through the mails and in retail outlets as an anorectic agent (appetite suppressant). A panel convened as part of the FDA OTC drug review concluded that PPA was effective and safe when used as an anorectic over-the-counter agent. Notwithstanding that the overwhelming majority of medical opinion considers the use of anorectic drugs as an inadequate approach to promoting permanent weight loss in obese individuals, there was and still is little data to support the conclusion that PPA is an effective anorectic drug. More to the point of this discussion, there is the data just described to suggest that PPA is not as safe as the panel imagined. Part of the problem is that the panel is made up of a group of people highly qualified in their particular areas of concern. Unfortunately, none of these areas appear to be concerned with clinical pharmacology and with toxicology.

Footnotes at end of article.

Testimonials and claims by the manufacturers of PPA containing diet aids notwithstanding, there is no reliable evidence to suggest that PPA is an efficacious anorectic agent. There is a preponderance of evidence to indicate that mishap associated with PPA use by the elderly is a foreseeable possibility. There is just no redeeming feature of the over-the-counter diet preparations which justifies the potential hazard they present to the elderly population.

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Ms. **Oakar**. Thank you very much. Dr. Mueller?

STATEMENT OF DR. SHIRLEY MUELLER

Dr. **Mueller**. I am Dr. Shirley Mueller. I am a neurologist. I practice at Indiana University School of Medicine where I'm an associate professor. I'm director of the neurology section at Wisher Memorial Hospital. I'm also a member of the National Heart, Lung, and Blood Institute Advisory Committee on Atherosclerosis, Hypertension, and Lipid Metabolism. I am lead author of 11 original papers relating to hypertension.

I think that our time would be spent most productively if I would develop for you how I became interested in this problem. About 2 years ago I saw a 16-year-old girl who came into our emergency room who had a seizure. She related that 20 minutes prior to having this seizure she had taken a look-alike pill, a pill made to look like amphetamine. But when we analyzed it, in reality it contained phenylpropanolamine, caffeine, and affedrine.

After that, we saw 10 more patients in our emergency room with similar sorts of problems.

Of the 11 patients, two had seizures, four had severe headache associated with an elevated blood pressure, and the remainder had psychiatric problems. All of these patients related having taken a look alike pill within an hour before the event, the event being psychiatric problem, the severe headache, or seizure.

Nine of these patients had their gastric contents or urine analyzed for presence of drugs, and phenylpropanolamine and caffeine were found. So, we're talking about—Mr. Lantos, are you coming? I want you to hear this. We're talking about not a controlled study, but a retrospective study here. And we did have an apparent cause and effect, since we were able to identify in the urine or gastric contents the drug, and the patient related to us that they had, indeed, taken a drug they called a look alike pill. We analyzed what was in their gastric and urine contents and found phenylpropanolamine, caffeine, and related it to the symptoms.

Now, look alike pills are different than diet pills. Look alike pills are immediate release and many of the diet pills are time release. Immediate release can be more dangerous because there will be a rapid elevation in drug level. So, the time release could be safer.

We were interested in looking at this problem under controlled conditions, a prospective study.

We've done two things. One is that we have looked at animals, and the other is that we submitted a grant to the National Institutes of Health to look at the effect of phenylpropanolamine on human blood pressure.

Let me go over our animal data. We have looked at hypertensive animals and animals with normal blood pressure. The hypertensive animal that we have looked at is the animal called the spontaneously hypertensive rat, which is like the human with a essential hypertension or hypertension of unknown etiology.

In the spontaneously hypertensive rat, when it is administered six times the recommended dose per weight, the percentage of cerebral hemorrhage that we note is 18 percent. This is markedly different than the normotensive animals where we do not note cerebral hemorrhage. A cerebral hemorrhage is associated with an elevation in blood pressure in these hypertensive animals.

Now, we're using six times the recommended dose. However, we only studied about 20 animals. If we could expand our study to, let's say, 100 or 200 or 400 animals and use the recommended dose, it is possible that we would find an increased incidence of cerebral hemorrhage in the normotensive animals.

Animal research does directly relate to human research in that our bodies do not act totally differently from animals. We plan, as I mentioned, in the future to look at humans and determine the effect of phenylpropanolamine in allowed doses by the FDA on blood pressure in humans. We have not yet done that.

I'd like to talk with you today about why some individuals suffer medical complications related to an elevated blood pressure when they take diet pills containing PPA. I think you may have something that was handed out to you. It's a summary of what we're going to be talking about over the next few minutes.

The most obvious reason is that the reaction is peculiar to the individual, that is, idiosyncratic. Since most of the literature relating to PPA complications is anecdotal, this must be considered a possibility.

If the reactions reported are idiosyncratic, these occurrences cannot be avoided. Then the crucial question is benefit/risk. If the benefit is high the risk may be worth the benefit. I think someone else will direct his testimony to the benefit. The risk may be high and we'll talk about that in points two and three, so that effectively eliminates the possibility of idiosyncratic reaction.

Another possibility explaining the occurrence of medical complications is that consumers ignore the diet medication package warning, which is reproduced below. You all are familiar with this. It's been read to you several times. I won't do it again.

Since consumers think that over-the-counter drugs are safe, they often do not read the package insert. Thus, at-risk groups, such as people with heart disease, may take the pills on occasion and suffer complications. The solution to this is that consumer education should be undertaken on over-the-counter drugs so that the public reads and follows the directions.

However, even with a large effort in this regard, some people would still ignore the package insert. Thus, again, we are back to benefit/risk ratio.

Yet another possible explanation for complications is that individuals with a normal blood pressure become acutely hypertensive when taking the allowed dose, and suffer complications. Studies sponsored by the drug companies themselves support an elevation in blood pressure secondary to PPA. Dr. Young has already alluded to this when she showed you her graph, and I'd like to show you another graph taken from a study sponsored by a drug company that was submitted to the FDA.

Before going over this graph I just want to talk a little bit about the blood pressure studies. They're hard to do. They're not easy to do. A lot of the studies that have been sponsored by the drug companies, in all probability, have not been done accurately. Likewise, a lot of studies done by others are not done accurately. But let's go over some of the reasons that they may not have been done accurately.

Our blood pressure varies during the day, so it's important that the blood pressure is always taken at the same time of day in any individual.

Also, in any one individual the blood pressure will be different than in another person. So, the very best study is to relate the blood pressure, taking a sugar pill, to the blood pressure while on the drug. In other words, my blood pressure may run 120 over 80, someone else's may run 100 over 60. So, we need to compare each of us to ourself on and off the drug.

Also, in order to take blood pressure accurately, the last of three blood pressures must be averaged to determine the accurate blood pressure. In many studies the blood pressure is taken only once, and this leads to an exaggerated high initial blood pressure, which means that all of the other blood pressures may be off if all of them are compared to an early morning initial blood pressure.

Also, an expert must take the blood pressure because it is very difficult to do. Someone who has been trained according to the recommendations of the American Heart Association should do it.

The study that is shown in this graph was done according to some of the criteria we've just talked about in terms of taking blood pressure accurately and doing studies accurately. In this study, sponsored by one of the drug companies, the blood pressure shown on the vertical axis and the time on the horizontal axis.

The systolic or greater of the two blood pressure readings is shown above, and the diastolic or lower of the two blood pressure readings, is shown below. The solid line represents the blood pressure after taking 75 milligrams of phenylpropanolamine. The dashed line, after taking a sugar pill.

Although most blood pressure points did not differ between placebo and PPA, at 4 hours there is a wide difference. In some individuals the difference in pressure between drug and placebo would have been far greater than illustrated here, since this is the average of the groups. And Dr. Young, I think, presented some examples to you.

Since rapid, dramatic increases in blood pressure can lead to headaches, seizures, stroke, and death, it is possible that in a group of several thousand people, rather than the 53 studied here, that such a reaction could occur. In addition, a number of people have a mild, periodic, asymptomatic, elevation in blood pressure when taking PPA, as demonstrated in the graph.

Although the concept of periodic elevations in blood pressure can lead to sustained hypertension is controversial, there is evidence to support that concept. This would mean that periodic elevations of blood pressure secondary to PPA could, over time, cause damage to body organs that may lead to permanent damage.

In order to settle these questions, a cardiovascular review committee, expert in the physiologic effect of periodic elevations of blood pressure on the body, should examine the existing data on PPA-containing drugs in order to deliver their opinion on its safety.

In addition, some individuals may be accurately sensitive to the interaction of commonly used drugs and PPA. For example, hypertensive crises have been reported in individuals on indomethacin, an aspirin-like compound, who took PPA-containing drugs.

Indomethacin is not listed as a contraindicated drug to take with PPA on the package insert. Thus, animal research is needed to determine what interaction, if any, can occur between PPA and indomethacin. Indomethacin has been shown to enhance blood pressure elevation in the presence of another drug similar to PPA, so a precedent for such research has been substantiated.

Another explanation for complications is that an at-risk group, not covered in the package warning, take the pills and subsequently have complications. One assumption made with the package warning is that everyone with high blood pressure is aware of his condition. We know that one-half of the 23 million Americans that have hypertension are not aware of it. So, a large potential at-risk group exists.

In addition, since hypertension is more common among overweight individuals and overweight individuals are more likely to consume diet pills, the at-risk group is even larger than would be expected. Women on birth control pills may be at special risk because they gain weight while on the pills and therefore are susceptible to taking diet pills.

At the same time, significant increases in diastolic and systolic pressure occur in these women.

Ms. **Oakar**. Doctor, could you summarize so that we can get to some questions?

Dr. **Mueller**. I'd be delighted to do so.

These at-risk groups need to be studied under normal environmental conditions. Let me explain that to you. The studies that have been done so far, sponsored by the manufacturers of diet pills, study the people while they are eating, for the most part. They're not allowed to drink caffeine drinks. We know that caffeine elevates blood pressure independently, that caffeine is contained along with PPA in many diet pills.

In addition to that, people aren't allowed to smoke. Smoking is a normal environmental condition as well. Smoking can elevate blood pressure. So, we need to study people with normal blood pressure in the at-risk group that are exposed to the diet pills, plus normal environmental conditions. If this were done, I think an even more dramatic rise would be noted than our graphs.

[The prepared statement of Dr. Mueller follows:]

PREPARED STATEMENT OF SHIRLEY MUELLER, M.D., DIRECTOR OF NEUROLOGY, REGENSTRIEF HEALTH CENTER, INDIANA UNIVERSITY SCHOOL OF MEDICINE, INDIANAPOLIS, IND.

Let me describe to you my experience regarding phenylpropanolamine (PPA) and PPA/caffeine. Eleven patients were seen in our emergency room with psychiatric symptoms, headaches and seizures related to ingestion of PPA-containing "look-alike" pills. "Look-alike" pills are made to look like amphetamines but in reality contain PPA, caffeine and sometimes ephedrine. The patients are described below. This chart was taken from Mueller, SM. Neurologic Complications of Phenylpropanolamine Use. Neurology 33: 650-652, 1983.

Complications of Phenylpropanolamine (PPP) "Look-Alike" Pills

Pts	Sex	Age	History plus physical exam	Drug analysis
1	M	38	Took 5 to 6 pink pills thought to be "speed;" one hour later, developed headache and was tremulous	PPA plus unidentified substance in urine
2	M	37	Took two "hits of speed;" one hour later, developed severe headache and vomited	PPA in urine
3	M	22	Took three "black beauties;" three hours later, complained of severe headache; ECG abnormal	PPA in urine
4	M	21	Took two "black beauties;" headache, tremor, diaphoresis, and nausea plus vomiting followed; pupils were 8 8 and poorly reactive	PPA plus caffeine in urine
5	F	19	Took "pink ladies" and 15 "speckled pups" thought to be "speed;" one-half hour later, developed a headache, diaphoresis, and vomiting; ECG abnormal	PPA and caffeine plus unidentified substances in urine
6	M	29	Took at least two "black beauties" and smoked two joints; began acting in a bizarre fashion, including undressing at the airport	PPA in urine
7	F	25	Overdose of unknown white pill; acute psychosis superimposed on chronic undifferentiated schizophrenia followed	PPA in urine
8	M	13	Attempted suicide by hanging	PPA in urine
9	F	17	Took several "black beauties," and alleged sexual assault	PPA in urine
10	F	17	Took a "pick-me-up" pill believed to be amphetamine; twenty minutes later, experienced two generalized seizures	The "pick-me-up" contained 50 mg of PPA, 200 mg of caffeine, and 25 mg of pseudoephedrine
11	F	27	Took a "diet pill" believed to contain "speed;" a generalized seizure was noted 11 hours later	The "diet pill" contained PPA, 200 mg of caffeine, and 25 mg of ephedrine

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Drug Anlysis. Gastric contents or urine were analyzed by thin-layer chromatography in nine patients. Positive findings were confirmed by gas chromatography. Phenylpropanolamine was identified in each case. In two patients, caffeine was also found, and an unidentified substance was discovered in two others. This particular drug screen rules out more than 130 drugs as possible components of the substance being analyzed (Kenneth Ryder, M.D., Director, Chemical Pathology, Wishard Memorial Hospital, Indianapolis, Indiana, personal communication). No amphetamines were found. In the patients with seizures, gas chromatography analysis of pills identical to those ingested showed phenylpropanolamine, caffeine and ephedrine.

In the five patients with headache, blood pressure was elevated for the average age (27 ± 2 years) (mean ± SEM). The arterial pressure was 175 ± 10 over 92 ± 4 mm Hg (mean ± SE) with the average for age being 116/70. Three of these patients vomited and two were tremulous. Two patients had electrocardiographic abnormalities. All of these abnormalities resolved after a few hours in the emergency room or after admission to the hospital.

It is reasonable to implicate PPA as the cause of the symptoms of the patients described since none had experienced previous similar episodes, all had taken PPA in the preceding hours, (and denied other drugs) and most other drugs that could cause such symptoms were absent from urine and gastric contents. Furthermore, the time course of symptoms was compatible with a drug reaction.

Although most of the patients reported in this study had taken more than the allowed quantity of PPA or PPA/caffeine, the symptoms that resulted illustrate complications that can occur secondary to PPA or PPA/caffeine. The major difference between the "look-alike" pills and diet pills is that the former often are in an immediate release form where the majority of the PPA and PPA/caffeine diet preparations are in a time release form. Thus, the effect of the "look-alike" pills may be more acute since absorption would not be delayed and side effects would be more likely to occur.

We have performed animal studies which indicate that hypertensive animals are more susceptible to brain hemorrhage after six times the allowed dose/weight (FDA standards) of PPA/caffeine administration than animals with a normal blood pressure. The presence of brain hemorrhage was determined by a neuropathologist in blinded fashion using histologic techniques. One can conjecture that hypertensive humans are also "at risk" when taking PPA/caffeine. Since a large percentage of our hypertensive population is not aware that they have hypertension and since hypertension is a more common among overweight individuals susceptible to taking diet pills, the "at risk" group is large and not readily identifiable. In addition, subject variability would potentially make some people more susceptible to complications from allowed doses of PPA/caffeine than others.

Ms. **Oakar**. Thank you very much, Dr. Mueller. Dr. Prout?

STATEMENT OF DR. THADDEUS E. PROUT

Dr. **Prout**. Thank you. I'm Thaddeus E. Prout, associate professor of medicine at the Johns Hopkins University School of Medicine and chairman of the Department of Medicine at the Greater Baltimore Medical Center. I've also been made chairman of the Pharmacy and Therapeutics Committee of the American Society of Internal Medicine. I'm a fellow of the College of Clinical Pharmacology and presently president of the Society for Clinical Trials, whose sole purpose is to maintain the integrity of good scientific work.

I might also say that I should put in two disclaimers. One would be that I didn't have anything to do with that last study that was purported to come from the Hopkins. I also talked to them about it and argued with them about averaging their data and thereby nullifying some important results.

The other is that I speak for myself today and not for these societies of which I am a part.

I wanted to remind Mr. Pepper before he left that I have also just been appointed to the planning and evaluation task force of the National Council on Patient Information and Education, which is one of her favorite committees.

A great deal has been said this morning, and I wish to use my spare minutes as others have by responding to some of the comments already made, and submit my written testimony for the record.

Ms. **Oakar**. Without objection.

Dr. **Prout**. I'm no stranger to this controversy. I've been at it, longer than most here, for some 15 or 20 years. My most recent involvement has been in association with the attorney general's office of Maryland, when a company from your favorite State, Ms. Oakar, had the temerity to come into Maryland and give false advertising. We went at them and won.

Ms. **Oakar**. Great.

Dr. **Prout**. The important thing, however, is that this is very wasteful of time, as the respondents for the FDA and for the Postal Service, and others, have shown. You need only to change the name of the company and change the name of the drug and you can be back the next morning at sunrise with the same product under a different label. It's that simple to circumvent the process. I think we are going to have to look at the problem, as you have said, in a general way, and try to find a means by which the whole PPA industry can be attacked generically.

The question of anecdote and risk/benefit has come up repeatedly. Anecdote is, I suppose, a way of introducing the concept that if the numbers are small enough, they don't matter. I knew that the users of that term would decry that interpretation, but the fact of the matter is that it's difficult to give mathematical significance to small numbers when there is a large unaccounted denominator.

We all remember when the problem of strokes in young women taking the pill was an anecdote, and it took some very sophisticated epidemiologic studies to nail that one down. There's no way to run a controlled clinical trial on the side effects related to PPA. Indeed, I personally do not feel that it would be entirely ethical to do a long-term study in this field, knowing the problems as we do.

I think that we need to deal with this in terms of risk/benefit ratio because I think we've established, through the dialog between Mr. Wortley and Dr. Young from the Center for Science in the Public Interest, that the trivial degree of weight reduction that can be expected from the use of these pills, could not really be called effective, and over a lifetime of obesity the loss of a temporary quarter or a third of 1 pound, after 6 weeks of therapy, is hardly "effective therapy."

I make that point strenuously because in talking about a risk/benefit ratio, if there is no benefit, then no risk is warranted, none whatsoever. It is an *x* over zero and the risks mathematically, is infinite and in the practical world of medicine is just not acceptable.

I would like now to talk about what is wrong with what has been reported to come from the ad hoc committee of the FDA on PPA.

First, their decision concerning the safety of PPA came from the safety review that was actually done concerning the short-term use of these pills for their decongestant effect. They did not look at safety themselves, except to review other data very quickly, and to go on to the question of efficacy. They then accepted as efficacious a "statistical difference" as describes in the studies that were proffered by the producers of these pills, the authenticity of which, again, I think we always have to bring into question.

What we found between 1972 and 1974, when I was chairman for the FDA of a conmmittee looking at the effect of amphetamines on weight reduction, was that the best foot that industry could put forward was none too good. The FDA looked at over a thousand studies, volume after volume. We then came down to 200 controlled clinical trials that were worthy of scrutiny. Here we again came up with the same trivial evidence that the difference in weight loss was much less than 1 pound per week averaged out over the studies which were only 6 to 8 to 12 weeks duration. One cannot call this effective weight reduction.

We also found evidence of the lack of safety, and on this basis, we first recommended that all drugs with abuse potential be scheduled as dangerous drugs. When FDA failed to act on this recommendation, we agreed that obesity should be taken away as an indication for the use of amphetamines. We had already won the fight in Maryland and this had already been done there as well as in Canada by the time the FDA got around to accepting this final recommendation. That act by the FDA essentially stopped the traffic in amphetamines as a weight-reducing excuse for proffering these over the signatures of reputable physicians. So much for the moment for the risk/benefit ratio and the evidence of efficacy.

I'd like to go on quickly with the remaining time to simply talk about safety and, once again, the word anecdote comes up. I don't think we can laugh off the Horowitz Study from Australia that showed that 30 percent of the people who were young and healthy came up with a significant and dangerous increase in the diastolic blood pressure.

I also think that the evidence from the Hopkins, when it's looked more seriously, shows that there are a number of people in that study as well that had significant hypertension. So these are not just unusual samples they confirm the danger.

A third of the young people who take this drug in the recommended therapeutic dose, have dangerous elevations of their diastolic pressure. That is no longer anecdote. This relates to the known physiology of these drugs, which Dr. Schwartz could describe much better than I. This known physiology fits in with all of the side effects that we are now reported as happening to people using these drugs.

My own scientific evidence is also a bit anecdotal in the sense that a former resident physician who found himself interested in going into a remote area, and I apologize to any people here who are from North Dakota, if I offend them, but he went out into Fargo, N. Dak., to set up practice. There, in the course of 6 months, he found seven people in his accident room that had severe amphetamine-like effects from PPA. Now, is that anecdote? No.

Dr. Albert Dietz published this in the Journal of American Medical Association. It's a well-known study and it's a respected study. And how do you think that an over-the-counter drug became this product of abuse in Fargo, N. Dak.? Certainly it didn't take a large drug push to get it out there. That came about by real anecdote. Any high school child knows that if you take enough of these drugs you can get a high, and seven of them appeared in Al Dietz' accident room in a 7-month period.

I think that's a little beyond scientific anecdote and I'd like to call the panel's close attention to it.

We are also saying that this has to be looked at in terms of the aging population. To the aged, I think all of us will agree, youth is beautiful, slim is youthful, and that they are interested in weight reduction is an axiom. You have some information Ms. Oakar, that shows that they are, in fact, using these drugs. They will continue to use them. They will continue to use them as long as they are advertised for the reduction of weight. They are ineffective and the risk is unacceptable and untenable.

I think that what we are watching here is what I might call the all-American over-the-counter flim-flam. They are promised something like is "Take out your savings and buy our drugs and we will make you youthful and young and slim again." This is a fraud and it should be dealt with as a fraud. I don't believe that we are talking, as Mr. Lantos has asked us not to talk about withdrawing these medicines, from all over-the-counter use.

However, I do think he would agree that if his family and his young relatives are using ineffective drugs for the wrong reason, they should be taken off the market for that indication so that his family can save their money. I think we can now look to the indications for use of these medicines and whether they should or should not be allowed to be used for obesity. I would say then that we may have two additional actions to take: One, make them prescription drugs, if they are to be used for obesity. Two, make them schedule 2 drugs. Here I differentiate to man schedule 2 of the Dangerous Drug Act, not the categories of the FDA that have been bantered about. Schedule 2 means that a doctor has to write the prescription. He can't renew it over the phone. It is controlled. These should be controlled substances, and, momentarily to return to a previous comment. Ms. Ferraro was not too far off when she said, "There's good news and bad news." Indeed, maybe, "there is bad news and bad news." These drugs are not called controlled drugs, but they should be, when we look at the experience around the world in their use. But prescription schedule 2 labeling would not be necessary if we take away obesity as an indication for their use.

Finally, this Select Committee on Aging, looking at the relationship of drugs to the aged, looking at the way information is to be given out on drugs, must look very carefully at a new danger that is rapidly approaching, and that is the danger of allowing drug houses to advertise directly to the consumer for prescription drugs as well as for the over-the-counter drugs. That may be considered to be another issue, but I beseech you to look at that issue very carefully as well.

Portions of the drug industry, not all to be sure, are very rapacious and they cannot be allowed to expose the trusting consumer to its high-powered promotional tactics unshielded.

I pause there and wait for questions.

[The prepared statement of Dr. Prout follows:]

PREPARED STATEMENT OF THADDEUS E. PROUT, M.D., ASSOCIATE PROFESSOR OF MEDICINE, THE JOHNS HOPKINS UNIVERSITY, AND CHIEF OF MEDICINE, GREATER BALTIMORE MEDICAL CENTER

Members of the Committee: I am Thaddeus E. Prout, M.D., Associate Professor of Medicine at The Johns Hopkins University School of Medicine and Chief of Medicine at the Greater Baltimore Medical Center. I have been asked to reflect on the use of drugs in the treatment of obesity.

I am no stranger to this problem. My concern began over a decade and a half ago and has allowed me to be a part of a battle against false advertising for drugs related to obesity which has been successful in all of those confrontations that actually came to trial. The most recent of the cases concerning phenylpropanolamine (PPA) was in association with the Attorney General of Maryland concerning a public hearing held on January 25, 1981, against the Consumer Publishing Company, North Canton, Ohio; National Pharmacals, Canton, Ohio; Richelieu Pharmacals, Canton, Ohio; and the president of the Consumer Publishing Company. A copy of the final order against the defendants is appended.

In addition, this will be my fourth appearance before a committee or subcommittee of Congress in association with misrepresentation of the therapeutic efficacy and safety of pharmaceutical products. I am chaiman of the committee on pharmaceutical agents for the American Society of Internal Medicine; a Fellow of the College of Clinical Pharmacology; and president, founding member, and member of the Board of Directors of the Society for Clinical Trials. All of these organizations have an interest in these procedures, but I do need to state unequivocally that I speak today not as their representative but from my personal study and conviction.

Further, I am a duly appointed member of the Planning and Evaluation Task Force of the National Council of Patient Information and Education under the leadership of a former and illustrious chairperson of this committee, the Honorable Paul G. Rogers. In the tradition of this committee, past and present, I am dedicated to the rational use of drugs of proven safety and efficacy.

The issues in most of the former battles have tended to concentrate on the question of the effectiveness of these agents, but I should like to begin, as I said before Senator Gaylord Nelson almost ten years ago, "The final judgment as to the efficacy of a drug is based on the benefits derived from the drug in contrast to the risks inherent in the use of that drug. This is frequently spoken of as the risk-benefit ratio. If there are no great benefits to be derived from the use of a pharmaceutical agent, there would seem to be little justification for the use of this agent since some risk is inherent in the use of any foreign chemical in human subjects. The use of pharmaceutical agents with harmful side effects and little usefulness cannot, in fact, be justified."

There is nothing new about the attempt to use PPA for the treatment of obesity. In 1948 the late R. A. Williams, M.D., later Professor of Medicine, chairman of the Department of Medicine, Washington State University, and the foremost endocrinologist in the United States, stated, "Of eight amphetamines tested, PPOA (PPA) ranked seventh while Dextroamphetamine was first as regards their relative effectiveness in ability to suppress the appetite."

For the next twenty years, PPA was used principally as a nasal decongestant since it was not effective for weight reduction. In the mid sixties research funded by individuals interested in promoting the unlikely possibility that this was an effective drug in the treatment obesity appeared, and a controversy over the effectiveness of PPA as an anorectic agent immediately followed.

In 1976 an advisory panel of FDA reviewed the literature on the safety and efficacy of PPA and concluded that PPA was safe for adults as a cold remedy in specifically recommended doses provided there were no contraindications. In 1978 a second advisory review panel was convened by FDA for the purpose of reviewing the evidence on PPA as an aid to weight reduction for over the counter use. A tentative statement for the advisory review panel issued in December 1978 concluded that "such products are safe and effective for OTC use when the amount of Phenylpropanolamine contained in the product is within the recommended per dose (25 to 50 mgs.) and daily dosage (not more than 100 mg.) amounts." In reaching this conclusion, the panel depended on the previous findings of safety for cold remedies and on unpublished reports for evidence of efficacy.

In the treatment of obesity, the prototype medication among the amphetamines and its congeners, of which PPA is a minor member, has always been Dextroamphetamine. In 1974 an extensive review was undertaken of data available from legitimate pharmaceutical firms concerning the efficacy and safety of amphetamines as a treatment for obesity. Over one thousand reports were reviewed from which two hundred studies were analyzed by the committee of which I was chairman. There was evidence of only trivial weight loss by individuals taking these powerful drugs over those taking only placebo. The committee was able to conclude that the differences in weight loss between the two groups of patients was confined to a few pounds over a period of from eight to sixteen weeks. Moreover, this difference was already lessened with time over even the short span of this study. Subsequent review of these medications following failure of the committee's recommendation to be enforced led to a recommendation that obesity be withdrawn as an indication for the use of these drugs, and this has been accomplished.

When the FDA Advisory Review Panel on Miscellaneous Internal Drug Products gave its report on PPA in 1979, it relied heavily, as noted previously, on the earlier report of the advisory committee of the FDA for evidence of safety as it was applied to PPA as a cold remedy. Evidence of efficacy for the treatment of obesity was based on reports which are largely unpublished. Although the FDA labeled this a "Tentative Report", the FDA has, by its silence, tacitly allowed the tentative conclusions to become public policy. as a result, both sales and profits more than doubled for one company alone between the first nine months of 1979 and the same period in 1980. Sales and profits have continued upward since.

Earlier it was noted that PPA stood seventh in a list of amphetamines as to potency in relation to its ability to control appetite. We have seen that the most potent of these agents yields only trivial reduction in body weight under controlled studies. Thus there is no scientific justification for the finding that a product one seventh to one tenth as potent as the major drugs in this field could succeed in counter distinction to the parent compound.

Turning now to the question of safety, an additional note of caution must be raised. Encouraged by manufacturers through false advertising, the use of PPA can be dangerous. The medical literature contains many reports of serious adverse effects following the use of this medicine. There is evidence that these drugs have been associated with acute lysis of muscle cells with secondary renal failure (JAMA 248:1216, 1982); severe elevation of blood pressure with myocardial damage (Br. Heart J. 47:51, 1982), cardiac arrhythmias (Clin. Toxicol. 7:573, 1970; Can. Med Assoc. J. 119:729, 1978); chest pain in normal patients (Med. J. Austral. 2:497, 1978; Lancet, 2:60, 1980); cerebral hemorrhage (Med. J. Austral. 2:258, 1959); psychic reactions to even a small dose of PPA such as mania and hallucinosis (A. J. Psychiatry 138:392, 1981; JAMA 245:601, 1981); as well as street abuse, seizures, and death from overdosage (JAMA 245:1346, 1981). Since under-reporting of all adverse drug effects is well documented, there can be no question of the potential dangers inherent in the use of this medicine.

From this review one can agree with Bennett that "any amphetamine with anorexic properties has the potential for causing untowards CNS side effects regardless of the manufacturer's claims" (Psychosomatics 4:327, 1963). In brief, no drug has been shown to have even trivial effects on appetite which was at the same time safe. The two effects are completely interlocked.

As an over the counter drug, PPA may be obtained by anyone without regard to special risk factors. This is of special concern in regard to the aging patient. These drugs which do little to control weight are especially dangerous in this group. Obesity increases with age and is associated with hypertension, cerebral vascular disease, heart disease, and diabetes. In addition, in their pursuit of youthful appearances, the aging population has become a susceptible group for the false advertisement related to the use of these drugs. These are the individuals at risk for central nervous system symptoms, cerebral vascular accidents, hypertensive crises, myocardial infarction, congestive heart failure, arrhythmias, and hyperglycemia.

I began by pointing out that I have been involved with a "one-on-one" confrontation with single manufacturers concerning the advertisement of single name drug products, but I have come to realize that this does little to resolve this problem. Delays of court action, appeals, and eventually the changing of the company name or the company product all serve the producer at the risk of the consumer. Action of this committee in the creation of legislation to prevent these abuses will do much to change this picture. Not only can this prevent the direct abuse of the consumer by a rapacious drug industry but it might also become the prototype for further reforms concerning drug advertisement generally. Unfortunately serious consideration is being given currently to allow the drug industry direct access to the consumer for all drugs through advertisement. Expansion of their legal right to do this would be a grievous error on the part of Congress or of the FDA. The example which we are discussing this morning in relation to PPA and specifically as it relates to the aging population is but a small portion of the problem that will develop if the right to direct advertisement is expanded. This committee should consider its role in preventing the abuse of the population most likely to be harmed by excessive advertisements.

Ms. **OAKAR**. Thank you very much, Doctor.

Dr. Ramey?

STATEMENT OF DR. JAMES RAMEY

Dr. **RAMEY**. Ms. Oakar, thank you for inviting me to speak today. My name is Dr. James Ramey. I'm a physician and I specialize in endocrinology and metabolism. I'm on the faculty of George Washington Medical School and I'm a consultant to the National Institutes of Health and to the Veterans' Administration Hospital.

It's my view that the over-the-counter diet medicines containing PPA should be removed from the market because they are neither efficacious nor safe. As others before me have said, they are particularly of danger to elderly patients.

In reviewing the studies purporting efficacy, I was wondering if any of the people who have done any of those studies would be willing to take a group of 65-year-old overweight people, not measure their blood pressure before they started the study, and give them phenylpropanolamine for 6 weeks to see if they lose weight and to see if anything bad happens to them. That study has not been done and I would predict that it would never be done because the drugs look to be unsafe enough that no responsible investigator would be willing to take the risk.

Now, why do I think that they're not efficacious? The gold standard for the treatment of obesity is that the weight loss has to be sustained for at least 1 year and probably 2 years. Obesity is a chronic disease that lasts, generally, for the lifetime of the person once they become obese. It's like high blood pressure. No one would advocate that a drug be sold for the treatment of hypertension that lasted for 6 weeks and then you stopped taking the drug. Because hypertension is a chronic disease which needs to be treated lifelong, as does obesity.

So, in evaluating any scientific study that's presented to you about the treatment of obesity, you have to see whether the weight loss has been sustained for 1 year or 2 years.

Now these drugs, as you know, the studies last generally between 4 weeks and 8 weeks. There is no study of any of these over-the-counter medicines that documents sustained weight loss for at least 1 year, and therefore, none of these studies, no matter how well done, are scientifically valid for the treatment of this chronic illness.

Now, given that the studies don't meet the gold standard, which in my testimony I have submitted in writing, that gold standard is presented in all the textbooks of endocrinology and metabolism, and none of them advocate using any kind of medicines for the treatment of obesity because none of them have been shown to be effective. They don't even mention these kinds of medicines, I might add.

Given that, look at the short-term studies that the drug companies, by and large, have presented as evidence that these drugs are effective, in the short run, for a period of 2 to 3 months. What astonished me, and I've read, I believe, every study that's been published in this matter, what astonished me, first of all, is that I've never heard of any of the journals that they have been published in. Including the International Journal of Obesity, which I have now heard of.

And the reason is when I was doing scientific research on drugs, what you did first when you did a study was you submitted it to the New England Journal of Medicine, and if they rejected it, then you sent it to the Annals of Internal Medicine, and if they rejected it you went down the list until you found somebody that would publish it, because if you didn't publish it, you didn't get promoted.

Well, I never got down to the International Journal of Obesity. On the other hand, I'm now in private practice.

If you look at the scientific validity of these studies, the reason that they haven't gotten into the New England Journal of Medicine is that they are poorly done studies. Many of them actually haven't even been published. They've just been submitted to the Food and Drug Administration. If you look at the way they do their controls, if you look at the way they do their statistics, most of them you can't even figure out whether the statistics are good enough because they don't give you enough information in the study.

So, scientifically speaking, the studies that purport to show that they caused some weight loss are bad studies and shouldn't be used for spending $200 million a year.

Now, given that, look at the advertisements on television. If you look at the advertisements on television you would think that if you took those drugs for a little while you'd get to be as slender as I am. Well, the fact is that that's what the drug companies would like you to think from their advertising. If you actually look at the studies which they used to purport to demonstrate weight loss, the maximum amount of weight loss, on the average, is about one-half pound a week.

Now, I see probably, in my practice of a dozen years, I've probably seen 400 or 500 people who come to me as a specialist in the treatment of obesity. Now, if I told one of those 250-pound people sitting across from my desk that under my expensive and sophisticated regimen at the end of 3 months that they would be 5 pounds lighter, they would stand up, walk out of my office, and refuse to pay my bill.

The fact is if the public knew that they wouldn't lose very much weight, even in the short run, and that they would be back to the same weight in the long run, they wouldn't buy these medicines.

In treating all these people with obesity, I must say that I'm very bad at treating patients with obesity. In every good scientific study looked at, the success rate is no bigger than 5 percent. And I'm no better than anybody else. Hundreds of patients that I've seen, they usually come to me fairly late on, because I specialize in that disorder. Almost all of them have taken over-the-counter diet medicines and almost all of them lost a couple pounds, and none of them are any lighter by the time they get to see me as a specialist.

So, they don't meet even the most minimum standards, it seems to me, of effectiveness. And they are dangerous. And I won't go into the details because people before me have done so. But it's my judgment that they are particularly dangerous in the elderly, because the elderly have a much higher incidence of heart disease and cerebrovascular disease, and to subject them to the risk of taking a medicine which has no benefit, it seems to me, is entirely unjustified.

And the elderly that I'm most concerned about, given that I am a big city doctor, are the elderly poor, of which there are a large number in Washington, D.C., and if you go and look at the drugstore windows in the ghettos in this town, that's where you see the big advertisements for the over-the-counter diet medicines. You don't see them in Spring Valley.

And the elderly poor are the people most likely to take over-the-counter diet medicines, and they are quite likely to not be under medical supervision because they can't afford it. And, as a consequence, they are the least likely people to know that they have high blood pressure and heart disease and should avoid those medicines.

So, and therefore, I think that these medicines should be taken off the market, since they are absolutely not efficacious, and therefore, as my predecessor said, since there is no benefit, no risk is acceptable.

Thank you.

[The prepared statement of Dr. Ramey follows:]

PREPARED STATEMENT OF JAMES N. RAMEY, M.D., ASSOCIATE CLINICAL PROFESSOR, GEORGE WASHINGTON UNIVERSITY

The most significant nutritional disease in the United States is obesity. Obesity contributes to heart disease, diabetes, hypertension and lipid disorders. It is an extremely widespread disease and though it has been with us for as long as humanity existed, it has only been a problem in wealthy countries where people can afford to eat more than their bodies burn. The cause of obesity is still unknown. We do not know why most people overeat. There have been a host of possible explanations given, such as early childhood overfeeding, hereditary disorders, hormonal disorders and disorders of the part of the brain that controls eating. As yet, none of these possibilities have been definitively proven to cause obesity. In part, because we do not know the cause of obesity, we have been unable to develop a cure.

What would be the definition of cure of obesity, a chronic disease which kills millions of Americans a year and which causes countless others to suffer shame because of our youth-oriented, slender-oriented society? Any cure for obesity must be a long term cure. Obesity is a chronic disease. One is not obese for a day, or a week, or a month. One is obese generally for one's entire life. No expert in obesity considers any treatment for obesity as being effective, much less being a cure, unless it can cause substantial weight loss that lasts at least a year or two.

Any modality which causes a small amount of weight loss that lasts a few weeks is, by the definition of experts in obesity, an ineffective treatment. If we compare obesity to hypertension, we have to realize that no one would consider a reasonable treatment for hypertension, which is a chronic life long disease, a treatment which lasted three to four weeks and which had never been proven to last longer than a couple of months. The old standard for evaluation of therapies for obesity looks at sustained weight loss of at least one year, and preferably two years.

Using that standard, no treatment for obesity has been effective in large populations of patients for more than five to ten percent of patients. The most successful methods for the treatment of obesity are methods that motivate patients to eat less, in a balanced diet. Programs such as Weight Watchers have in general been the most effective because they combine behavior modification with a reasonably decreased caloric intake. The object is to change people's eating habits so that over the long run they eat less. Since obesity has as a large part of it a psychological component, almost any program of weight loss which appeals to popular imagination works for a short period of time. Thus, fad diets recur in the American population. I first began practice ten years ago when the Atkins diet was popular. More recently, there was the liquid protein diet and most recently is the Scarsdale diet. All of these diets work and all of the nostrums and medicines work in the short run because people are motivated for psychological reasons to lose weight in the short run. What is needed is a treatment which will work in the long run, and that generally is behavior modification in which people learn to eat differently.

The hope has been that helping people to start out losing weight with some drug or gimmick will enable them to change their dietary habits and lose weight over the long run. This hope has not been fulfilled. There is no way to lose weight other than a life long plan of eating less than one wants to. These facts have made treating obesity very frustrating for the physician, not to mention the patient. An honest physician can tell his or her patient that the patient will have about a ten percent chance of sustained weight loss at one year if they go on his program of behavior modification and a balanced caloric reduction. If psychotherapy, group therapy, sophisticated dieticians and a gimmick or two are thrown in, the program might be slightly more successful. I do not have any gimmicks, and I in fact now do not encourage people who are overweight to come to me for treatment as I am just as unsuccessful as anyone else. They see me in the desperate hope that there is something wrong with their hormones, but there seldom if ever is.

I have seen hundreds of patients who are overweight. I have cured very few, and I have disappointed many. Hormones have always been normal.

Most of the patients that I see in my practice have already failed at miltiple diets and multiple gimmicky programs. Many have been to "fat doctors" and have been treated with shots and drugs which lasted only a transient period time. Almost all have tried over-the-counter appetite suppressants containing phenylpropanolamine. None has achieved weight loss of more than a few pounds that has been sustained for more than a few weeks. The major anorexiants are amphetamine-like agents and these drugs presumably exert their effects at the level of the hypothalamus. It is probable that they have a modest effect in promoting short-term weight loss in certain individuals. However, they are effective only for a period of a few weeks and problems of habituation, addiction and generalized drug abuse limit their usefulness. However, none of these agents treats the underlying eating disorder so they are, therefore, of little use in maintenance of weight reduction.

"The major problem in the treatment of obesity is not weight reduction but maintenance of the reduced weight." Provided the therapist works hard and long enough, most motivated patients can eventually lose weight. Unfortunately, only the rare patient maintains the weight loss permanently. Obesity is an eating disorder and the underlying mechanisms are not reversed by limiting food intake.

A quotation from the *Textbook of Endocrinology* by Williams (1982 ed) says "an appetite suppressant, usually amphetamine derivatives, are of limited utility, since their effect is transient and rarely leads to more than a 10 percent weight reduction. Since the treatment of obesity is life-long, such drugs have no demonstrable role in the long term management of obesity."

Thus, it has been demonstrated that any short term treatment of obesity which cannot be demonstrated to last for significant periods of time, usually defined as one to two years, is no treatment at all. Then, for evaluating any treatment of obesity which is going to be approved if not granted FDA approval, the treatment must be demonstrated to last for at least one year. No good study of obesity treatment demonstrates that any modality in a statistically significant way will lead to substained weight loss. Certainly no data suggests that amphetamine-like derivatives such as phenylpropanolamine will lead to sustained weight loss. If they do not meet this standard of efficacy, then by my definition, they are ineffective drugs and should not be sold as if they were effective.

It is given that with a little help starting out with weight reduction due to the drugs, people will learn new dietary habits. This has not been proven and in fact is exceedingly unlikely since it does not happen with any of the stronger amphetamine drugs.

Accepting for the moment that these drugs do not meet the long term standards that the scientific community will require for a weight reduction agent, let us see whether these drugs really meet the public's standard for a weight reducing agent. Contrary to what the package inserts and the advertisements would make people believe, the over-the-counter diet suppressant containing phenylpropanolamine appear to cause a very small amount of weight reduction. I have reviewed all the studies that were submitted to the FDA when it had its original hearings in the 1970's. I reviewed several studies that have been published since then. The astounding thing, from the public's point of view, is that they in fact document that very small amounts of weight reduction are achieved with these medicines. Studies were conducted in which there was frequent visits to the clinics, where doctors or other health personnel were seen, so there was a great deal of phychological support for the weight reduction effort which always included dieting plus taking the medicine. There was thus a large effect of the non-drug therapy that accompanied the drug. Therefore, in order to attribute any of the weight loss to the medicine you have to subtract what the control group, the group that did not get the medicine, lost. Over six weeks, which is the average duration of the studies, the average person lost 2.7 lbs more that the control group. If I told a patient coming to my office that over a six week period they would lose 2.68 more than they would lose if I merely prescribed sugar pills, they would get up, walk out of my office and refuse to pay my bill. If the public realized that over a six week period they would be lucky to lose 3 to 4 lbs, that they would probably not lose any more than that even if they stayed on the medicine and that they would be the same weight a few months later, almost certainly these drugs would not sell at all. The small amount of weight reduction actually achieved by these drugs in the studies is not realized by the people who buy the drugs.

It is astonishing to me that the FDA has accepted the studies that have purported to show that these drugs work, even in the short run. The studies which I have reviewed are generally of poor technical quality and have either not been published and are held by the drug companies, or have been published in obscure journals. Nowhere do you see any reports in the New England Journal of Medicine or the American Journal of Medicine or the Annals of Internal Medicine or any other reputable well-refereed presitigious medical journal. That is because these studies are poorly done. There is poor matching of patients to controls. Unless you can show that the treated patients and the patients taking the sugar pills were the same in most respects, you cannot show that any differences was due to the drug or to the differences in the patient populations. Frequently, the controls started off at different weights than the treated groups. The time periods used were very short; often three or four weeks, a pitifully short time to document weight loss since every program initially shows some weight loss. In these studies, the data given was quite inadequate to determine, from an objective point of view, whether the study was valid or not. The data only mentioned side effects casually and did not scientifically analyze the side effects. One study, in order to make its numbers statistically significant, excluded the treated patients in the study who had gained weight rather than lost weight. The studies had an unacceptably high number of drop outs from the program. One of the larger studies had a drop out rate of 34 percent of the treated group before the study could be treated.

Therefore, it is not at all clear to me that there has been any demonstrated efficacy of these drugs, even in the short run. If the studies that have been done are poorly done and are not convincing scientifically then one cannot say that these drugs even cause short term weight reduction. As I said before, even given that this is true, most of these studies show only a few pounds of weight loss over six weeks. This is clearly not acceptable to patients, and might be acceptable to doctors if the weight loss was sustained for a period of year, but this has never been demonstrated nor even alleged.

It is my contention that drugs sold over the counter should be efficacious and safe. The efficacy even in the short run has not been clearly demonstrated. The safety issue will be disscussed by others. I should point out, however, that a different standard of scientific validity should be given to fears of ill effects of over-the-counter medicines. Rigorous standards of proof that a drug is effective treatment should be required. Only in extremely valuable and therapeutically effective drugs can one afford to ignore reported of serious side effects. Many drugs which have serious side effects demonstrate them only in a few patients. To say that only 5 percent of patients had significant hypertension from taking these medicines may mean that hypertension may well not be demonstrated in a study in which an average of the blood pressure is done, which happens in many of these studies. The raw data in many of the studies is not available for scrutiny, but upon scrutinizing some of the data that has been made available, it is apparent that in some patients taking these drugs the blood pressure rises dramatically. Since these patients are not under medical supervision, whether or not the blood pressure goes up is not going to be known to the patient. The drugs are all amphetamine-like drugs and it is therefore likely that they cause some hypertension, and, as will be shown by other people testifying here, these medicines do cause hypertension in some people. They can also cause insomnia, irritability and a variety of other minor side effects. They can certainly aggravate hypertension in individuals who already have it. There have been many reports of serious side effects such as malignant hypertension, seizures, coma and serious psychiatric disorders precipitated by these drugs. While these are only case reports and are usually not clear reports, as people have been taking other medicines, they have to be taken seriously since these drugs are so widely available and are used by people not under medical supervision.

These medicines are particularly dangerous to older patients. Since these patients are more susceptible to the effects of hypertension in terms of rather modest rises in blood pressure precipitating heart attacks and stroke, it is particularly important that older patients be assured that these drugs do not harm them. I do not think that the package inserts warning that you should not take these medicines if you have high blood pressure are sufficient. People taking these medicines, especially older people, do not known that they have high blood pressure; they do not know that they have serious heart disease which may be aggravated by taking these stimulants. It is important, therefore, that these drugs not be promoted for older people. Furthermore, it is not demonstrated that older people benefit from minor decreases in weight, since frequently these people are dieting in order to treat hypertension or diabetes, and a few pounds of weight loss is not going to make a difference in those diseases. Particularly the unsuspecting elderly poor are at risk. They do not have access to medical care to find out if they have underlying disease if they know they are overweight and try to do something about it by taking one of these over-the-counter medicines which are so widely promoted.

It is my suspicion that these medicines are more likely to be used by people who cannot afford traditional medical care. They, therefore, turn to an unexpensive nostrum which might help them. These are people much more likely to have hypertension, heart disease that has not been detected previously because they have not been able to afford medical care. These are the people that are most at risk—the elderly and the poor—that I believe are most likely to take these medicines.

In summary, the over-the-counter diet medications containing phenylpropanolamine have not been proven to be efficacious for the treatment of the chronic disease known as obesity. They produce very little weight loss even in the short run and have the possibility for serious side effects and should not be sold over-the-counter in the United States since they are neither efficacious or safe.

Ms. **Oakar**. Thank you very much, Dr. Ramey.

Mr. Lantos?

Mr. **Lantos**. No questions, Madam Chairman.

Ms. **Oakar**. OK. Ms. Ferraro?

Ms. **Ferraro**. I have to tell you, looking at the four doctors there, I just want to ask you, do you schedule this as a house call?

My question is this: We have, and I'm going to pick up a little bit on what my colleague started to address to the previous panel. Just how much involvement is there with the elderly and these diet pills? You have indicated. Doctor, that thin is young and young is wonderful to the elderly, and we have had testimony from Dr. Mueller about high blood pressure, hypertension, is a problem with these diet pills, and if you put the two together you're going to have a problem, if you have elderly taking them. It seems like it's a schedule for disaster.

Are there a lot of people who want to get thin? I mean what's the size of the problem that we're talking about? Because I thought as you got older you eat less, as a matter of fact.

Dr. **Prout**. I take it you're addressing that to me?

Ms. **Ferraro**. Yes.

Dr. **Prout**. As one gets older, you may eat less, but you save more of it, and you do get fatter. I used to argue with another pharmacologist who stood on the other side of this question when he said that we had no right to be concerned about a young woman who only wanted to use PPA to get into a size 12 dress for her son's wedding. Well, we heard from a young woman this morning who did just that.

My rejoinder, without having a name to give to her at that time, was, "Yes, we do, if it's dangerous, and there's no benefit to be gained from it." And I continue to hold that position. Youth is slim and youth is beautiful to the elderly. They try to attain it. We also see this with exercise programs. Our accident rooms are sometimes filled by older people who think that if they exercise just a little more strenuously they will get there a little faster. So, the urge to do slightly more than is necessary is a common problem. They will take these agents, and in excess.

I don't have statistics on actual use but I believe our cochairman had some evidence that they were being used. I don't know how many.

Obesity, hypertension, arrhythmias, hyperglycemia, cerebrovascular diseases are all interlocked as part of the problem of aging, and it is about those people that we are very much concerned today.

Ms **Ferraro**. Let me ask what may seem a little bit far out as a question with reference to the elderly.

Dr. **Prout**. Not at all.

Ms. **Ferraro**. Have you ever seen an elderly person who has taken diet pills as an appetite suppressant because they could not afford to buy food?

Dr. **Prout**. I would always like to have that kind of confrontation because the price of the proper food is always less than they are presently eating. At the price of food in the supermarket today, I can save them a lot more money by having them restrict their eating to a proper diet than they can ever get by eating what they are eating and taking a magic pill. I can save them a lot of money.

The answer to your question is I have seen people say that they can't afford a diet, but not after they got the second half of my sermon.

Ms. **Ferraro**. Obviously it's not safe and obviously if you——

Dr. **Prout**. It isn't correct to believe that you must take the pills because it's cheaper, in order to lose weight.

Ms. **Ferraro**. No. What I meant, Doctor, is are there people, not to lose weight and put that in a comparison with the thousand calories—what I'm saying to you is are there people who come in who say, "I've taken diet pills because I just can't afford to buy food"? It does suppress your appetite, at least in the anecdotal. I remember that when I took them that 13, 14 years ago, I didn't eat anything at all. I mean, I was a total wreck but I didn't eat anything.

Dr. **Prout**. But we're talking about a lifetime of obesity.

Ms. **Ferraro**. No. No, I'm not talking about that. Forget the obese people.

Dr. **Prout**. You're talking about any kind of weight loss?

Ms. **Ferraro**. Any individual.

Dr. **Prout**. OK. Then we're talking about a third to a half-a-pound week over——

Ms. **Ferraro**. That's not what I'm talking about either. I'm talking about the individual coming in, an individual who is elderly, who comes in and has had a reaction to a diet pill, and is taking those diet pills and when you look at them you say, "What in God's name are you taking diet pills for?" and they say to you, "I'm taking it because I just can't afford to buy food. I've run out of my social security check. I've run out of whatever it is." I mean, do you ever have that kind of statement made to you?

Dr. **Prout**. Oh, I'm sorry to have misunderstood you.

Ms. **Ferraro**. I'm not talking about someone that wants to lose weight.

Dr. **Prout**. Do patients use pills to take away hunger because of an inability to buy food at all?

Ms. **Ferraro**. That's what I mean.

Dr. **Prout**. No, I've never had that experience and I doubt if any of the other physicians have, ever.

Ms. **Ferraro**. Has anybody on the panel ever had that experience with the elderly?

[No response.]

Ms. **Ferraro**. Have you, Dr. Mueller, had any experience at all with the elderly, because yours seem to be mostly young kids?

Dr. **Mueller**. I'm a neurologist and so I see strokes all the time.

Ms. **Ferraro**. Yes.

Dr. **Mueller**. And, of course, most strokes occur in the elderly. So, I see strokes all the time. In the elderly strokes that I have seen, none have taken diet pills prior to their stroke.

Ms. **Ferraro**. None. It's just an interesting thing. Thank you very much, Madam Chairman.

Ms. **Oakar**. Thank you. Did you want to respond, Doctor?

Ms. **Ferraro**. Oh, I'm sorry.

Dr. **Ramey**. I see a fair number of patients, in response to an earlier question, I see a fair number of patients in my practice who are over 65, who are overweight. My oldest patient in my practice is 107 years old and he weighs 225 pounds.

Ms. **Ferraro**. But again, the people I'm speaking about who might, where I was going was the necessity to take those pills in order to not pay for food, would not be coming in to see you, Doctor, as a private patient, at your fee schedule which you have just alluded to in your prior testimony. Thank you very much, Doctor.

Dr. **Schwartz**. I think there is something that, before we leave, you shouldn't lose sight of, because we have been talking specifically about the diet aids. Perhaps the best testimony I've heard this morning came from the chairman when he discussed the polypharmacy—the multiple drug therapy. Not only do we have difficulties predicting what toxicity of an individual drug is in an elderly adult, but if we combine that with the 7 to 13 other drugs that they are taking, we have an impossible toxicologic situation.

Dr. Mueller used the word "idiosyncracy," I think. An idiosyncratic response is an unexpected response. But I tell you that these are not idiosyncratic responses. We expect some toxic responses in the elderly adult, based on the number of drugs they are taking. This is especially true for drugs which have only toxic side effects and very little other benefit. And we're not talking about an unusual situation. It's entirely predictable.

Ms. **Oakar**. I do have some questions for each of you. Dr. Schwartz, you have really gone into the molecular structure of PPA. Is it accurate to describe it as a stimulant or isn't it? There was a court case and I believe, Dr. Prout, you were the expert witness or one of the witnesses about that case. Is it a stimulant or isn't it?

Dr. **Prout**. I agree that its central nervous system effect, and its stimulating effect are closely associated with amphetamine. It is very similar in structure and action to amphetamine. The closet similarity that PPA has to amphetamine is its effect on the blood pressure.

Ms. **Oakar**. Dr. Mueller. Did you have something?

Dr. **Mueller**. Nevertheless, the two may be correlated. What causes the central nervous system stimulation also probably leads, in part, to the elevation of blood pressure. In other words, the elevation in blood pressure is not totally a peripheral effect, but also a central effect.

Ms. **Oakar**. I see.

Now, Dr. Prout, you have been talking about PPA for years. Back in 1972, before Senator Gaylord Nelson's committee and his hearing you submitted a lot of testimony warning us about this problem, particularly as it relates to the drug industry. You were asked to be one of the witnesses in California about misleading advertising when the Attorney General successfully won this case against one of the drug companies that is in the market of producing over-the-counter diet drugs. Can you tell us a little bit about that case and what you found, in terms of advertising?

Dr. **Prout**. In terms of advertising or any other part of that case, I'm afraid I can't. It is one of the unfortunate facts that when you try to fight this problem on a one-on-one basis you run out of time, energy, and money, and I was not able to really help out in the *California* case because I couldn't afford to take the time to go out there. I was not part of that case.

Ms. **Oakar**. I see.

Dr. **Prout**. I was part of the case in Maryland, my home State, where I could just go downtown to do it. There too the stimulant question was raised. It is my feeling that these drugs are stimulants in the real sense of the word and that to ask that the word "stimulant" be taken out of the advertisement would would be contrary to the pharmacology and would falsify it even more.

In our Maryland case, for example, we were concerned that the public was not being told that there was a stimulating effect. The manufacturer leaned heavily on the fact that there was "no caffeine" and stated therefore that the drug contained "no stimulant." But the amphetamine family——

Ms. **Oakar**. Now we have extra strength diet pills with caffeine.

Dr. **Prout**. That's right.

Ms. **Oakar**. They're on the market now.

Dr. **Prout**. But I was not in on the *California* case because I couldn't afford the time and effort.

Ms. **Oakar**. I see.

But you have been really pursuing this question for a long, long time. It must be very frustrating to you to see it still larger than ever.

Dr. **Prout**. My colleague on my right, Dr Ramey referred to some work that actually came out of Dr. Williams' Textbook of Endocrinology, either in 1980, or one of the earlier editions. As far back as 19 8 Dr. Williams was already doing work on these agents. I happened to be a house officer at the Boston City Hospital at the time and my entrance into endocrinology was in no small part due to the fact that Dr. Williams was there.

He found at that time that PPA was less than one-tenth as strong as the grandfather of the whole family dextroamphetamine, and that fact is one that I keep coming back to. When we looked at the best studies that industry could provide between 1972 and 1974, and couldn't find evidence that the most powerful drugs were efficacious in the treatment of obesity, it is scientifically impossible for me to believe that a drug's acting along the same pathways, that is one-tenth as strong and in addition is used in less than one-tenth the amount could be expected to get any kind of efficacious results.

Hence, I am very hard on the efficacy of this drug, in addition to its lack of safety. Yes, I have followed the track of this drug for a long time and I'm yet to see any evidence that it has any benefits whatsoever.

Ms. **Oakar**. Dr. Ramey, you made perhaps the strongest charges against the over-the-counter drugs. And you really attacked some of the studies that have been submitted to FDA in favor of these over-the-counter drugs. And so has Ms. Young. I wanted you to know that we do have another panel that is responsible for some of those studies.

If you're interested in them, they, I am sure, are going to be talking about their studies. If you want to stick around that would be fine. I think we'd be interested in hearing some of the specific questions. But you mentioned you had not heard of the International Journal of Obesity. Tell me, when doctors submit your studies, and Dr. Mueller, when you submit your studies, do you usually have a peer review before you get it published?

Dr. **Schwartz**. Dr. Ramey's portrayal of the various journals is absolutely accurate. I'm on Georgetown's Rank and Tenure Committee for the medical school and when we get into the publish or perish decisions we look at the quality of the journal, in which the faculty member has been publishing, and that quality is determined by the editorial policy and by the nature of the editorial board.

If the journal has room for 25 manuscripts a year and it gets 24 to be reviewed, you can see that it's not going to be very selective. So, Dr. Ramey is absolutely right. There are some journals at the bottom that are just trying to get whatever manuscripts they can get. I don't wish to portray the International Journal of Obesity in that way because I know nothing about it or its policy, and that would be unfair.

Ms. **Oakar**. Someone mentioned that some of the studies that have been submitted to FDA on behalf of the diet pill industry have never been published; they're just the individual statements of the doctors?

Dr. **Ramey**. They do a scientific study and they publish it in manuscript form and submit it to the FDA. One presumes that they have submitted them to one journal or another, but the fact is that several of them have not, in fact, been published.

Ms. **Oakar**. How about advertising? I was talking earlier about pressures being put on some of us and my staff. I was interested in a channel 5 story that I understood ran in New York by Betty Furness, who is kind of identified with the consumer movement. She did a series, and yet most of it was broadcast out of the New York station. And then before her series was over, in the New York Times, they printed an ad from one of the drug companies attacking Betty Furness, "Instant science by Betty Furness is no public service."

[The ad referred to follows:]

INSTANT SCIENCE BY BETTY FURNESS

IS NO PUBLIC SERVICE.

Now we have another evening news drug scare from WNBC-TV.

The target this time is phenylpropanolamine, or PPA.

You've probably never heard of PPA, but it's on sale over the counter in every drugstore in nasal decongestants and appetite suppressants.

It is estimated that 40 million people annually take PPA for a stuffy nose.

And 10 million take it in smaller doses to reduce their appetites—a proven way to battle bulging waistlines and health-destroying obesity.

Now comes Betty Furness with a 60-second sensation.

Some street people and TV personalities may think PPA gives you a high, but scientists know it's more likely to lower your appetite and dry up your postnasal drip.

What about these doctors on WNBC-TV's most recent pharmaceutical shocker?

Well, doctors, the normal way to report adverse drug reactions is to the FDA and to your colleagues in their scientific journals. Such publication allows scientists rather than newscasters to sort out the evidence. But some doctors have found it's easier to get on the tube with sensational charges.

Maybe such medical advocates want every drug to be a prescription drug. Who will pay doctors' bills then? Medicare?

WNBC-TV didn't have to scour the sidewalks for the facts about PPA. We provided Betty Furness with a bundle of published and unpublished scientific literature

We suggested she interview doctors and research scientists who have been studying PPA extensively at academic institutions, including the University of California, New York University, Johns Hopkins University and elsewhere.

Right now, the FDA is reviewing a 1979 report by its own *Advisory Panel on over-the-counter weight-control drug products*, which wrote: "The Panel concludes that phenylpropanolamine hydrochloride is generally recognized as safe and effective when used for OTC weight control in the dosage noted below."

Well, Betty, this hardly sounds like another headline health scare. In fact, thoughtful scientific journalism would have spared a lot of viewers something more to worry about.

We hope you'll tell your viewers a few of the duller sidelights on PPA some Wednesday or Thursday night, such as—it works. So far, clinical studies show it does help people lose weight, and its safety record is better than aspirin's.

Where does this leave you if you are concerned about your weight? Well, viewers in a free society must decide for themselves.

If you are concerned, write us and we'll send you a research report on PPA recently published in the *International Journal of Obesity* (1982) 6, 549-558.

Thompson Medical Company, Inc.
919 Third Avenue
New York, N.Y. 10022

Ms. **Oakar**. They went into all of the reasons why, which is obviously their prerogative. The curious thing to me was they only printed it for the Washington edition, not the New York edition where they could reach the people that heard the show. I want to ask why that was done. Also I want to ask the FDA people if they felt the ad was addressed to FDA. But FDA isn't here today. They can't come, they say; they're too busy.

And here we're talking about some pills, in general the over-the-counter pills, that affect millions of Americans. I am specifically talking about diet pills that are a $200 million industry, $10 million of which are consumed by Americans. We've had some witnesses who have suffered real serious physical problems because they took that stuff. And they don't have time to come today. And you mentioned, Dr. Schwartz, I believe, that you had had difficulty relating to them.

Dr. **Schwartz**. Yes. I want to make it quite clear that I have a great deal of respect for the FDA's current administration, because I know both the Commissioner and people who work with him closely. That, notwithstanding, there was, starting from about 1980, through about 1982 when I was especially active in this with the Postal Service, that I had a very difficult time in getting any interest on the part of the Food and Drug Administration in this problem.

We were primarily concerned with look alikes, but also with the diet aids that were advertised through the mail. It was only through the rather persistent and perhaps veiled threats of a lawyer in the Consumer Protection Division of the Postal Service that we were finally able to get information such as autopsy reports that had been gathered by FDA investigators. This information was needed in order to deal with the look alike problem and to pursue some of the successful prosecution that the Postal Service had on the look alike problem.

Ms. **Oakar**. Thank you. And thank all of you very, very much. Your entire testimonies will be submitted for the record and we will continue now with our final panel of individuals.

Ms. **Oakar**. We have invited various members of the industry. However, only one company responded, Thompson Medical Co., and they recommended that these members be part of our last panel. We're happy to have them. So, we do have a panel.

Dr. Silverman is a pharmacologist of Massachusetts College of Pharmacy. Would you, Doctor, come up and perhaps identify others who have also come with you? We would be happy to have all of the individuals.

PANEL 4—INDUSTRY OFFICIALS, THOMPSON MEDICAL CO., INC., CONSISTING OF DR. HAROLD I. SILVERMAN, PROFESSOR OF PHARMACY, MASSACHUSETTS COLLEGE OF PHARMACY AND ALLIED HEALTH SERVICES; DR. MATTHEW H.. BRADLEY, CARDIOLOGIST, MIAMI HEART INSTITUTE, MIAMI, FLA.; DR. CHARLES WINICK, PROFESSOR OF SOCIOLOGY, CITY UNIVERSITY OF NEW YORK; DR. RUDOLF E. NOBEL, DIRECTOR, CATHEDRAL HILL OBESITY CLINIC, SAN FRANCISCO, CALIF.; DR. ANTHONY CONTE, BARIATRICIAN, BEAVER, PA.; DR. MARIANNE SEBOK, PHYSICIAN, AFFILIATED WITH J. F. KENNEDY MEMORIAL HOSPITAL, FRANKFORD HOSPITAL AND ALBERT EINSTEIN MEMORIAL CENTER, PHILADELPHIA, PA.; DR. FRANK FUNDERBURK, THE BEHAVIORAL PHARMACEUTICAL RESEARCH UNIT OF THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE; EDGAR E. COONS, PH. D., PROFESSOR OF PSYCHOLOGY, NEW YORK UNIVERSITY; JAMES SCHREIBER, JR., JAMES SCHREIBER, SR., AND BARBARA RITZ

STATEMENT OF DR. HAROLD I. SILVERMAN

Dr. SILVERMAN. Ms. Oakar. We have a rather fine panel.

Ms. OAKAR. Would you all come forward, please?

Dr. SILVERMAN. Yes. Why don't I just bring our panelists all up to the front of the room?

Ms. OAKAR. That's fine.

Dr. SILVERMAN. I'll present my testimony and my introduction of the panel and then each one of these gentlemen and women will present their testimony.

Ms. OAKAR. That's fine. Could we try to get a few more chairs around the table. We're having a more difficult time accommodating all of you.

Dr. Silverman, would you identify for the record the individuals who are part of your panel, as well as yourself, please?

Dr. SILVERMAN. I'm sorry, Ms. Oakar, I did not hear you. A gentleman was talking to me.

Ms. OAKAR. I'm sorry. Would you identify the members of your panel? We would be very pleased to hear from each and every one of them.

Dr. SILVERMAN. I have a prepared statement for the committee. Let me first identify myself and then each of my associates.

My name is Dr. Harold I. Silverman. This is Dr. Coons, Dr. Conte, Dr. Bradley, Dr. Winick, Dr. Noble, and Mr. Funderburk. I believe that directly in back of us is Dr. Sebok.

Ms. OAKAR. Thank you.

Dr. SILVERMAN. My name is Dr. Harold I. Silverman. I hold a doctor of science degree from the Philadelphia College of Pharmacy and Science. I am a professor of pharmacy at the Massachusetts College of Pharmacy and Allied Health Sciences, and I am the executive director of its Pfeiffer Pharmaceutical Sciences Laboratories. My curriculum vitae has been provided to the committee.

I am acting today as the leadoff witness for a group of physicians and scientists. Many of us have given testimony to the FDA's advisory panel which found that phenylpropanolamine [PPA] was generally safe and effective as an appetite suppressant. Others of us have done new research in response to the Food and Drug Administration's request for research on particular aspects of PPA.

I would like to talk to you today about phenylpropanolamine, a drug I have studied and worked with for over 25 years. When I first became interested in PPA it had already been in use for approximately 20 years. In fact, the first medical report of its effectiveness as an appetite suppressant was published in 1939. Since that time a considerable amount of research has been carried out on phenylpropanolamine and contrary to some assertions that I have heard, we do know quite a bit about this drug, much of which is published.

First of all, what is PPA? We know that it belongs to the chemical family of phenethylamines, and this includes many important drugs. It shares similar chemical characteristics with ephedrine, amphetamine, and phenylephrine, with major exceptions. While amphetamine is a powerful stimulant, even at normal therapeutic doses, phenylpropanolamine does not exbibit any stimulant effects at all, at recommended dosage levels.

In other words, for all practical purposes, PPA is simply not a stimulant. The stimulant action of amphetamine carries with it a very high potential for abuse. PPA, on the other hand, has no abuse potential at all. This has been dramatically demonstrated in animal studies which compare the reinforcement properties of PPA to those of amphetamine and other drugs of abuse.

More importantly, studies of drug abuse patterns in humans have shown that phenylpropanolamine plays no significant role. Dr. Winick, an authority on drug abuse, will discuss this subject in greater detail.

Now, let's turn to the area and question of efficacy. Does PPA help you to lose weight? Most emphatically, yes, it does. In addition to the earlier literature, documenting the efficacy of PPA, over a dozen well-controlled clinical studies have now been submitted to the Food and Drug Administration.

This chart, which may not yet be uncovered, but—which is over to the committee's left, and which I helped prepare, summarizes some of these studies. As you can see, the average weight loss reported for patients who received and took PPA, was about 1.2 pounds per week, more than twice the weight loss than those that took a placebo. This means that if you take PPA over the recommended 12-week period, you can certainly expect to lose on the average almost 15 pounds.

A survey of almost 3,000 consumers who used PPA reported even higher weight losses. Of course, you have to reduce your intake of calories in order to lose weight, something most overweight people have a great deal of difficulty in doing. PPA, with its proven appetite suppressant qualities, can and does play a major role in helping overweight people change their eating habits, and this, thereby, leads to an increased and significant weight loss.

Finally, I'd like to address the all-important issue of safety. To date approximately 50 safety studies on PPA involving nearly 4,000 patients, have been submitted to the Food and Drug Administration. The results: No significant adverse effects have been reported in any of these studies.

There have been a number of isolated case reports, published in the medical literature in recent years, and these have attributed adverse effects such as sharp increases in blood pressure, heart rate, seizures, convulsions, psychotic episodes, and other serious problems to the use of PPA. When these reports are examined in detail, however, they invariably deal with frank overdoses, accidential or intentional, or combinations with other drugs. Or, situations where the actual dosage used could not be determined nor could it be confirmed.

These isolated reports need to be viewed in light of the hundreds of millions of doses of PPA that are safely consumed each year in this country alone as either appetite suppressants or as nasal decongestants.

The only report of adverse effects that claimed to be from a controlled study was carried out on medical students in Australia. This study reported significant elevation of blood pressure following the ingestion of an Australian PPA diet aid and a somewhat lower increase when a PPA nasal decongestant product was used. These unusual results can be partially explained by the fact that some of the dosages used in that study were considerably, considerably, higher than those recommended for use in this country.

In addition to which, it has never yet been clarified whether or not it was truly phenylpropanolamine that was used in that country. My own research never confirmed that phenylpropanolamine had been used.

More importantly, however, these Australian results had never been obtained before, nor have they been reproduced in any other study either in Australia or in this country. With this in mind I would only conclude that this study had serious flaws and should be discounted.

In conclusion, my own research on phenylpropanolamine and my extensive review and study of the medical literature has convinced me that this is a safe and efficacious product when used as directed. I am in complete agreement with the unanimous findings of the FDA advisory panel which stated: "After a thorough investigation that phenylpropanolamine is generally recognized as safe and efficacious when used for OTC weight control."

Thank you.

Now I'd like to introduce my colleagues at the table so that they can now provide a 1-minute statement, if I might have your kindness and indulgence.

Ms. **Oakar**. Fine. I'd be very happy to hear from each and every one of them.

Dr. **Silverman**. Dr. Bradley is from the Miami Heart Institute and may we first hear from Dr. Bradley, please.

STATEMENT OF DR. MATTHEW H. BRADLEY

Dr. **Bradley**. Thank you. I'm Matthew Bradley, M.D. I'm engaged in the private practice of internal medicine and cardiology in the Miami area. I'm vice president and trustee of the Miami Heart Institute. I'm a member of its research committee, and I serve on its publications and review committee.

As a reviewer of research, a conductor of original research, and as a cardiologist, I have been involved in blood pressure studies for some years. Currently, I am evaluating the safety of phenylpropanolamine or PPA, an ingredient in the over-the-counter aids and cough cold products used daily by millions.

In my study over 6 weeks, PPA was used in the treatment of obese patients with controlled, stable, hypertension. This study found no clinically significant differences in the patients' blood pressures or pulse rates at either the 75 milligram time-released dose or the thrice daily, 25 milligram dose.

We also found that PPA greatly reduced or eliminated hunger pangs and thus was effective in aiding the patient to lose weight. No side effects were reported.

I am now conducting a larger study on controlled hypertensives, and while the study is not complete, I can tell you on this side effect issue that none of the 28 patients who have completed this study have reported any adverse reactions.

From my own research, then, and the research I have reviewed, I can only conclude that PPA diet aids are both medically safe and effective. Thank you.

[The prepared statement of Dr. Bradley follows:]

PREPARED STATEMENT OF MATTHEW H. BRADLEY, M.D., CARDIOLOGIST, MIAMI HEART INSTITUTE, MIAMI, FLA.

Good morning, my name is Dr. Matthew H. Bradley. I hold a Bachelor of Science degree from Kent State University and an M.D. degree from Ohio State University. I am certified by the American Board of Internal Medicine and am a Fellow in the American College of Physicians, the American College of Cardiology and the American College of Chest Physicians. I am a member of the Board of Directors of the Miami Heart Institute and of the Research Committee of the Miami Heart Institute.

In addition to being a Clinical Instructor in Medicine at the University of Miami School of Medicine, I am engaged in the private practice of Internal Medicine and Cardiology in the Miami area.

I am also an active researcher in coronary heart diseases and have published a number of papers in such journals as The Journal of American Medicine and The Journal of Clinical Investigation.

In 1979, the FDA's Advisory Review Panel on OTC Miscellaneous Internal Drug Products submitted its findings that phenylpropanolamine (PPA) was "generally safe and effective for weight control." The Advisory Panel had reached this conclusion after four years of reviewing the literature and the data submissions and after listening to additional testimony. It was hardly a rush to judgment.

However, while the FDA was considering its Advisory Review Panel's finding, two studies were reported in Australia which suggested that PPA might increase patients' blood pressure. Accordingly the FDA asked researchers to conduct further study on this question.

I have been involved in this blood pressure issue as both a reviewer of research and as a conductor of original research. For that reason, I want to describe to you a pilot study that I have recenly concluded, a pilot study that led to a study presently under way.

The purpose of the pilot study was to evaluate the safety of PPA in the treatment of obese patients with controlled, stable hypertensive diseases. We selected 12 patients, varying in age from 25 to 67, all at least 10 percent overweight and all of whom were being treated for hypertension.

Why bother to study PPA's safety for hypertensive patients, when it is not recommended that they use PPA except under a doctor's care? Because scientists, doctors and the FDA want to be exceptionally careful, and testing extreme cases can be very informative.

The study found no clinically significant differences in the patient's blood pressures or pulse rates from when these patients began the study and when they finished it. Nor did we find any clinically significant differences in blood pressure or pulse rate at the one-half hour, one hour, 2 hour and four hour periods following the first medication dosage for the 25 mg, the 75 mg or the placebo doses. Nor did we find any significant blood pressure or pulse rate differences within treatment weeks, either.

Was the PPA effective? Yes, in both appetite suppression and weight loss. Ninety-three percent of the patients reported that they experienced none or only slight hunger feelings after receiving either the 25 mg or the 75 mg dose of PPA. But 71 percent of the patients reported moderate or marked hunger pangs after receiving the placebo doses.

When patients took PPA doses, they experienced a mean cumulative weight loss in excess of one pound per week. When they took the placebo, they experienced a mean cumulative weight loss of slightly more than one-half pound per week.

These results were obtained in a single-blind, crossover study that extended for six weeks. During the first two weeks, each patient took 25 mg of PPA three times a day. In the second two-week period, each patient took a placebo twice a day. In the last two weeks, each patient took a time-released 75 mg dose of PPA once a day. The middle two week period not only acted as a control period, but also to allow any PPA which might remain in the system to be washed out, thereby rendering valid the results of the final two weeks of the test.

Each patient was checked weekly for body weight, temperature, blood pressure, pulse, both degree and duration of appetite suppression and side effects. Every two weeks, each patient received a full physical examination, including an electrocardiograph while lying down, as well as blood pressure and pulse readings one-half hour, one hour, 2 hours and 4 hours after the initial dose that day.

Ten of the initial 12 patients completed the study. Two were discontinued from the study after two weeks, one because his hypertension was being controlled by a drug that violated the test protocol and the second because of previous time commitments. Neither of the two reported having any adverse reactions.

No patient reported, or was observed to have, any side effects.

I have moved into a large-scale study which is now in progress. It is far too early to report on that study. However, I can tell you that of the 28 patients who have completed the parts of the study utilizing 25 mg of PPA three times a day and the placebo, none have reported any side effects, either.

What my pilot study does demonstrate, though, especially for the concerns of this subcommittee, is that PPA diet aids are both medically safe and effective, even for those with stable, controlled hypertension.

Thank you.

Ms. **Oakar**. Thank you very much, Doctor.

Dr. **Silverman**. Now, before I introduce Dr. Charles Winick, an internationally known authority in the area of drug abuse, and if I can have your indulgence, Dr. Winick, we also have with us three consumers who, while they don't have any prepared statement, are available to the committee for questions, should there be any, and who have used appetite suppressants containing phenylpropanolamine finding them to be both safe and efficacious.

Mrs. Barbara Ritz is here. Mr. James Schreiber, Sr., and Mr. James Schreiber, Jr.

Now, let us hear from Dr. Winick.

Ms. **Oakar**. Would they stand up, at least, for us? So we can take a look at them?

Dr. **Silverman**. Thank you.

Ms. **Oakar**. Thank you very much.

We'd be happy to have their testimony for the record, if you would like, Dr. Silverman.

Dr. **Silverman**. Thank you very much. That would be fine.

And after the panel has concluded if they could come to the front and present a short statement, it would be very gracious of you.

Ms. **Oakar**. Fine.

Dr. **Silverman**. Dr. Winick from the City University of New York. Dr. Winick?

STATEMENT OF DR. CHARLES WINICK

Dr. WINICK. Madam Chairman and ladies and gentlemen: I appreciate the opportunity of appearing here before you today. My name is Charles Winick. I hold a Ph. D. in psychology and am a professor of sociology at the City University of New York Graduate Center, where I regularly teach courses in drug abuse. I am editor of the Yearbook of Substance Use and Abuse, and also a psychologist in private practice.

I hope to be submitting a written statement for the record, and I would like to summarize that for you now.

For more than 25 years I have been actively researching trends in drug abuse and I have supervised interviews with 160,000 drug abusers about the substances they take, the context in which they take them, and the gratifications which the drugs provide. I regularly track emerging substances of abuse and monitor the degree of their popularity.

In this connection, I have been following the use of PPA in the United States for some years. Let me make some summary statements about my conclusions on PPA as a substance of abuse and/or addiction. PPA does not meet the criteria for being a drug of abuse or addiction. It does not lead either to physiological or psychological dependence. It does not provide a rush or a high. The body does not develop a tolerance to it. It does not damage the organs of the body. And it has no significant dysfunctional effects.

Indeed, PPA is not a drug of choice or even a secondary drug of choice among drug abusers. In fact, in the Federal Government's most recent report from its Drug Abuse Warning Network [DAWN], PPA accounted for less than one-fifth of 1 percent of all the substances mentioned, and ranked 102d among those substances that were mentioned.

In just-completed national studies of trends in drug abuse among high school students and among the general population, sponsored by the National Institute of Drug Abuse, PPA was not cited as a drug of abuse.

In conclusion, all available clinical and epidemiological data consistently demonstrate that PPA has not been and is not a drug of abuse.

[The prepared statement of Dr. Winick follows:]

PREPARED STATEMENT OF CHARLES WINICK, PH. D., PROFESSOR OF SOCIOLOGY AT THE CITY UNIVERSITY OF NEW YORK

Good morning. My name is Charles Winick. I hold a Ph. D. in social psychology from New York University and am a psychologist in private practice. In addition, since 1966, I have been professor of sociology at the City University of New York Graduate Center, where I regularly teach courses on trends in drug abuse. I am also an active researcher in the drug abuse field. Among the sponsors of my studies have been the United States Senate Subcommittee on Juvenile Delinquency, the National Institute of Mental Health, the National Institute of Drug Abuse, the White House Special Action Office for Drug Abuse Prevention, the World Health Organization, and the American Association Against Addiction.

At the American Social Health Association, I started what is now the National Clearinghouse on Drug Abuse Information. My articles on drug abuse have appeared in the Encyclopedia Britannica, the American Medical Association's Today's Health Guide, and the Yearbook of Substance Use and Abuse, of which I am editor.

For more than 25 years, I have been interviewing drug abusers about the substances they take, the context in which they take them, and the gratifications which drugs provide. My interviews have ranged from experimenters to dysfunctional abusers. In addition, I regularly track emerging substances of abuse and monitor the degree of their popularity.

For this reason, I have been following the use of phenylpropanolamine in the Unites States for some years, and I would like to comment on its potential for abuse.

For a substance to be a candidate for abuse, it must meet specific criteria. These criteria include physiological and/or psychological dependence that can lead to a compulsive desire for the substance. In addition, substances of abuse can have dysfunctional effects on the user.

Phenylpropanolamine does not meet these criteria.

Phenylpropanolamine does not lead either to psychological or physiological dependence. It does not provide a "rush" or a "high." The body does not develop a tolerance to it. It does not damage organs of the body, and it does not have significant dysfunctional effects.

Certainly phenylpropanolamine is not a drug of choice among drug abusers. It is not even a secondary drug of choice—for example as a substitute for amphetamine when the latter is not available. Indeed, the federal government's most recent report from its Drug Abuse Warning Network, for July-September 1982, ranks phenylpropanolamine 102nd among drug mentions. Phenylpropanolamine accounts for less than one-fifth of one percent of the mentions.

Nor did the government's most recent national survey of patterns of drug abuse find phenylpropanolamine to be a drug of abuse. All the available data indicate that phenylpropanolamine is unimportant in terms of both the incidence and prevalence of abuse.

Occasionally, as you know, a particular drug or combination of drugs has a group of users in one area—like glutethimide and codeine ("Hits") in the Newark area now. But, there is no community with a concentration of phenylpropanolamine users. In fact, at a national conference on epidemiology of drug abuse conducted in Rockville, Maryland, in December 1982 with presentations from 19 major cities, not one presenter cited phenylpropanolamine as a substance being abused.

The appearance of phenylpropanolamine in lists of drugs of abuse or in occasional anecdotal reports is likely to reflect one of three things:

(1) polydependent persons who are taking many substances at the same time, one of which is phenylpropanolamine;

(2) users of "look alike" substances; or

(3) persons taking more than the recommended dose or hypersensitive individuals with idosyncratic allergies.

Epidemiological studies should be able to confirm the role of polydependence, the decline of "look alikes," and a drop in accidental overdoses. In the case of the polydependent, a negative effect may be attributed to phenylpropanolamine when it actually resulted from one of the other substances or from synergism among substances. Negative consequences from "look alikes" usually stem from the ephedrine-caffeine and not from the phenylpropanolamine component.

Since this three-way combination is now illegal, there should be a sharp drop in phenylpropanolamine mentions attributable to this source.

As the public has more experience with the use of phenylpropanolamine in appetite suppression, we can confidently expect that the number of reports of toxic reactions will decline, analogous to the experience we have had with other substances which increased their popularity in a short period of time.

On the subject of these reports of toxic reactions, I have reviewed a recently published report from the Intermountain Regional Poison Control Center in Utah, which raises some questions about their validity. The authors of the study, which involved 70 patients who had taken overdoses, either intentionally or accidentally, of PPA-containing products stated:

"The lack of serious side effects in either the cases with only PPA or combinations of PPA with caffeine raises questions about the serious reactions noted in earlier published reports."

I am submitting a copy of this report to the committee and ask that it be included in the record (Exhibit A).

Speaking as a clinician, researcher and epidemiologist, I believe that phenylpropanolamine is trivial and insignificant as a drug of abuse and that it will become even less consequential in the future.

Thank you.

SCIENTIFIC REPORTS

Papers published in this section are reviewed by at least two qualified referees for accuracy, scientific soundness, experimental design, data analysis, and interpretation. Papers accepted may result from original research, critical literature reviews or well documented field investigations.

AN ESTIMATION OF THE TOXICITY OF NON-PRESCRIPTION DIET AIDS FROM SEVENTY EXPOSURE CASES

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The American compulsion to be slim, combined with the conclusions of a non-government advisory panel's recommendations in March of 1979 indicating benzocaine and phenylpropanolamine (PPA) in over-the-counter (OTC) weight control products to be safe and effective, have increased the use and the availability of these drugs in American homes. Weight control products obtained without a prescription fall into two classes: sympathomimetic-containing products and those without. Those without may contain vitamins, methylcellulose, benzocaine, fructose, lethicin, and grapefruit extract. The sympathomimetic-containing weight control products may contain any of the above with PPA alone or combined with caffeine. Table 1 lists some of the common commercially available products. While PPA is reported safe in doses for weight control (1), there are limited data about the toxic effects of PPA when taken in overdose (2-5). There is mounting evidence of serious toxicity when taken in combination with other drugs (6-8) and in hypersensitive persons using normal doses (9-20). Caffeine is not an innocuous drug (12,22). Although serious toxicity from caffeine is rare, its danger is well documented (23-28). Caffeine in combination with PPA will contribute to the toxicity in possibly both overdosage and in regular doses.

The purpose of this report is to describe the range of presenting signs and symptoms following ingestion of OTC sympathomimetic-containg weight control products and to estimate the toxic dose and sequelae from such overdose.

METHODS

The patients for this prospective study were either children or adults who had ingested a non-proprietary sympathomimetic-containing weight control product. The study period was for 5 months. Patients who met the following criteria were included: History of ingestion of a sympathomimetic-

Table 1. Commonly Available Over-The-Counter Stimulant-Containing Appetite Suppressant Products

Product	Manufacturer	PPA (mg)	Caffeine (mg)	Other Substances
Anorexin Pick Your Menu Weight Loss Program				
Anorexin	SDA Pharm	25	100	--
Anorexin One-Span	SDA Pharm	50	200	--
Appedrine Max Strength	Thompson Medical	25	100	*
Appress Tablets	North American	25	100	--
Ayds Appetite Suppressant Droplets (0.6 ml=12 drops)	Purex	25	0	--
Ayds Extra Strength (Red Capsule)	Purex	75	200	--
Ayds AM/PM Appetite Suppressant Capsules	Purex			
Yellow Cap.		50	200	--
Blue Cap.		25	0	--
Canadex Capsules	Central	75	200	--
Codexin	Arco Pharm	75	200	*
Coffee Break Cubes Weight Reduction Plan	O'Connor Drug	37.5	0	--
Coffee-Off	Westport Pharm Sales	25	0	--
Coffee, Tea, and a New Me	Thompson Medical	25	0	--
Control Capsules	Thompson Medical	75	0	--
Control Drops/ 0.2 ml=4 drops	Thompson Medical	25	0	--

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*Present address: Valley West Hospital, 4160 West 3400 South, West Valley City, Utah 84120

Table 1 (cont)

Product	Manufacturer	PPA (mg)	Caffeine (mg)	Other Sub-stances
Cool Down Tablets	Westpoint Pharm Sales	25	0	--
Day Trim	Westpoint Pharm Sales	75	0	--
DelcoPro	Delco			
Tablets		25	0	--
Capsules		75	0	--
Dexa-Bar Capsules	Republic Drug	50	200	--
Dexader Plus	Republic Drug	75	200	--
Dex-A-Diet Capsules (formerly Dex-A-Diet II)	O'Conner Drug	75	200	--
Dex-A-Diet Drops (formerly Dex-A-Diet II)/0.6 ml	O'Conner Drug	25	0	--
Dex-A-Diet Lite Capsules	O'Conner Drug	75	0	--
Dexatrim Capsules	Thompson Medical	50	200	--
Dexatrim Ex Strength Capsules	Thompson Medical	75	200	--
Dexatrim Caffeine-Free Ex Strength Capsules	Thompson Medical	75	0	--
Diadax	O'Conner Drug			
Capsules		50	0	--
Tablets		25	0	--
Dietac Pre-Meal Diet Aid Drops/0.2 ml=5 drops	Menley James Labs	25	0	--
Dietac Pre-Meal Diet Aid Tablets	Menley James Labs	25	0	--
Dietac 12 Hr Diet Aid Capsules	Menley James Labs	50	200	--
Dietac Max Strength Capsules	Menley James Labs			
Once-A-Day		75	0	--
Twice-A-Day		37.5	0	--
Dietcap	L Perrigo	50	200	--
Dietcap without Caffeine	L Perrigo	75	0	--
Dietguard 14 Day Diet Plan	Whitehall Lab	25	0	--
Diet Trim	Pharmex	Present Amount?	0	+
Dyna-Slim WL	Weight Loss Group	75	0	--

Table 1 (cont)

Product	Manufacturer	PPA (mg)	Caffeine (mg)	Other Sub-stances
Fluidex Plus	O'Conner Drug	25	0	+
Grapefruit Chewable Diet Tablets	Sharpe Nationals	60	0	+
Grapefruit Diet Plan With Diadax	O'Conner Drug			
Tablets		10	0	+
Capsules		30	0	+
Grapefruit Diet Plan With Diadax Chewable Tablets Ex Strength	O'Conner Drug	25	0	+
Grapefruit Diet Plan With Diadax Ex Strength Vitamin Fortified Continuous Action Capsules	O'Conner Drug	75	0	+
Hungrex	Allegheny Pharmacal	25	0	--
Hungrex Plus	Allegheny Pharmacal	33.33	66	--
Obestat	Lemmon	75	0	--
Odrinex - See Super Odrinex				
Permathene-12	Allegheny Pharmacal	75	140	--
Phenopro-75 Ex Strength	M K Lab	75	200	--
PPA - Max Strength	Allegheny Pharmacal	75	0	--
Pro-Dax 21	O'Conner Drug	75	0	--
Prolamine Capsules	Thompson Medical	37.5	140	--
PVM Appetite Control Capsules	J B Williams	75	0	--
PVM Appetite Suppressant	J B Williams	25	0	--
Slip and Slender	Allegheny Pharmacal	25	0	--
Slimplan Ex Strength Plus	Whiteworth	75	200	--
Spantrol	North American	45	50	+
Spantrol Ex Strength Plus	North American	75	150	+
Super Odrinex	Fox Pharmacal	25	100	--

Table 1 (cont)

Product	Manufacturer	PPA (mg)	Caffeine (mg)	Other Substances
Thinz Drops/ 0.2 ml=5 drops	Alva Amco Pharmacal	25	0	+
Thinz Back-To-Nature Tablet Reducing Plan - Ex Strength Formula	Alva Amco Pharmacal	75	+	--
Thinz-Span Max Strength	Alva Amco Pharmacal	75	+	--
Trim Down	Ajax Drug	75	0	--
Unitrol Diet Plan Capsules	Republic Drug	75	0	--
Vita Slim Capsules	Thompson Medical	50	0	+
X-11 Reducing Plan Tablets	Porter and Dietsch	25	25	+

containing weight control product, subsequent treatment, follow-up or evaluation by the poison control center staff or at a treatment facility. All ages were included. For patients evaluated and treated at home, telephone contact was maintained to resolution of symptoms or for twelve hours, whichever was longer. Patients were excluded from the study for the following reasons: ingestion of significant amounts of other drugs concommitant with the study drugs, lack of satisfactory history, and patients whose condition was later determined to be of another origin.

RESULTS

During the five months of the study, a total of 70 patients met the criteria of the study. The data from these patients form the basis of this report. Thirty-four percent of the patients were male (24) and 65% were female (46) despite a mean even sex ration in the 0-5 age group. The ages studied ranged from 9 m to 20 y (mean 5.0 y, SD = 5.74 y) for males, and 1½-54 y (mean 13.4 y, SD 12.1 y) for females.

The patients were divided into two groups: those involved with accidental childhood ingestion (9 m to 8 y) and the self-destructive or substance abuse patients (age 11-54 y). The ages and sex ratios of the former group were near equal with no striking differences. In the intentional group there is a 1:6.5 ratio of males to females and a distribution of ages in females which indicates the misuse of these substances is not limited to a discrete age group. The preponderance of females using these substances compared to males may be indicative of the more likely purchaser of diet aids. Young adults (ages 13-21 y) comprised 30% of all cases and almost 75% of the intentional group. Children ages 0-5 accounted for 56% of all cases seen.

Table 2 is a list of the non-proprietary products involved in the 70 cases. In some cases several products were involved. Dexatrim® (regular or extra-strength) products accounted for 71.4% of all the products involved suggesting ready availability in the homes from either advertising or sales success.

Both Dexatrim® products are combinations of PPA and caffeine. Ten cases (14.3%) involved only PPA, the remaining 60 cases (85.7%) involved combinations of both PPA and caffeine in varying doses and amounts. No products with only caffeine were involved.

None of the PPA-only cases involving children under 14 developed symptoms although small amounts were generally ingested. All of the patients over 14 who ingested only PPA developed mild symptoms. The symptoms described in these four patients included nausea, vomiting, abdominal cramps, headache, hot flashes, diaphoresis, dyspnea, irritability and tachycardia (140 beats/min). In patients with only PPA involved, the onset of symptoms was usually within 30 min to 1 h and the duration of symptoms averaged 13 h. Only one patient required hospitalization. An estimated ingested dose in the symptomatic patients was 17.5 mg/kg.

The fixed dosage ratios of PPA to caffeine (Table 1) ranges from a low of 1:1 to a high of 1:4. Therefore, at a given dose of PPA the amount of caffeine present in the product may vary by a factor of four. This makes defining the dosages of either PPA or caffeine in combination difficult with the available data. Table 3 describes symptomatic patients by age with the estimated doses of PPA and caffeine ingested and the dose to weight relationship. All patients over age 13 were symptomatic regardless of the history of ingestion. Children in the 0-2½ y age range generally took

Table 2. Brands of Diet Aids Involved in Seventy Human Poisonings.

Brand Name		Exposures	%
Appedrine Maximum Strength		1	1.4
Control		5	7.1
Dex-A-Diet II		1	1.4
Dexatrim		29	41.4
Dexatrim Extra Strength		21	30.0
Dietac:		6	8.6
Pre-Meal Diet Aid Tablets	1		
Maximum Strength Once-A-Day	1		
Pre-Meal Diet Aid Drops	1		
12 Hour Diet Aid	3		
Hungrex		1	1.4
Permathene-12		1	1.4
Phen-Pro-75		1	1.4
Super Odrinex		1	1.4
X-11		2	2.9
Unknown		1	1.4

Table 3. Symptoms, Treatment and Dosage of Phenylpropanolamine/Caffeine Combination by Age

Age	Total	Symptomatic Number (%)	Onset of Symptoms (hr)	Duration (hr)	Estimated Dose Ingested By Symptomatic Patients				Ipecac Given	No Treatment
					PPA		Caffeine			
					mg	mg/kg	mg	mg/kg		
0-2	19	3 (15.8)	2	2-4	133	10.5	460	40	9	10
3-5	14	2 (14)	<1	3	150	9.8	500	34	3	11
6-12	2	1 (50)	<2½	12	300	8.2	800	32	0	2
13-21	19	19 (100)	1	12±9.48	575	[illegible]	1400	26	5	10
>22	7	6 (85.7)	1½	20±14.5	235	5	680	15	1	4

only 1-2 dosage units.

The type of symptoms and frequency noted in the study patients are listed in Table 4. Headache, nausea or vomiting, nervousness, and tachycardia were most often seen. Almost all symptoms appeared within the first two hours. In approximately one-third of the cases, symptoms persisted for up to 6 h, another one-third of the cases had symptoms for up to 10 to 12 h, and the remaining one-third had symptoms persisting for widely varying lengths of time.

Physician evaluation was required only 18 times (22.85%). Seventy-seven percent of the time the problem was managed at home with only demulcents to delay absorption or the induction of emesis using syrup of ipecac. Of the patients managed in the hospital, only two required hospitalization, 64% were discharged from the emergency department in less than 4 h, and the remaining discharged in an average of 8.25 h. The duration of treatment in the health care facility and the therapy performed are noted in Table 5.

DISCUSSION

Phenylpropanolamine is a sympathomimetic amine structurally similar to amphetamine, ephedrine and metaraminol. The pharmacologic actions of PPA are described as a direct alpha adrenergic effect and an indirect acting amine producing release of norepinephrine from storage site at nerve endings (8,11). Its structural formula protects it from rapid degradation allowing for extended duration of action from oral administration (20). Common side effects from overdose associated with PPA include hypertension (2,4,12-14,19,20), severe headaches (2,4,11-13,19), blurred vision (13), confusion (4,5,13,16,18,19), vomiting (2,12,19), and seizures (2,5,13,20).

Caffeine is a naturally occurring alkaloid which is rarely associated with serious adverse reactions or fatalities (22). A possible explanation for the low frequency of serious reactions is the high incidence of gastritis and prominent central nervous system side effects with relatively small doses. Pharmacologic effects on the central nervous and digestive systems can be seen with as little a dose as 50 mg. A therapeutic dose is near 100-200 mg (27). Caffeine stimulates the cerebral cortex, the thalamus, the vasomotor and respiratory centers (21, 22,24-27). Cardiac stimulation resulting in a variety of arrhythmias have been reported (21,23,25). The combination of caffeine with PPA produces a pharmacologic synergism accentuating some action of each drug.

The dose at which symptoms developed for PPA alone was 17.5 mg/kg. This is not suggestive of a minimum toxic dose, rather a dose that predictably produced symptoms in the study patients. When PPA/caffeine combinations were involved in children (age 0-5), a toxic dose for PPA was close to 10 mg/kg (average total dose was 140 mg). The caffeine doses averaged 37 mg/kg with an average total dose of 480 mg producing symptoms. All adults studied were symptomatic, suggesting that early demonstrable clinical findings are expected and that symptoms are not a good early descriminator between the low versus the high end of toxicity.

Table 4. Symptom Complaint and Frequency

Symptom (May be more than one symptom per case)	No
Nausea or vomiting	20
Nervousness	12
Headache	10
Tachycardia	8
Dizziness	6
Drowsiness	3
Weakness	3
Disorientation	2
Shortness of breath	2
Hot flashes	1
Increased urination	1
Flushed	1
Numbness of hands	1

Table 5. Treatment Performed and Duration of Time in the Health Care Facility (Number)

Duration of Time in the Health Care Facility (hr)	
<4	9
4-8	4
8-14	1
>14	2
Treatment Performed	
Ipecac	9
Activated Charcoal	5
Cathartic	4
Intravenous hydration	3
Phenobarbital	1

The lack of serious side effects in either the cases with only PPA or combinations of PPA with caffeine raises questions about the serious reactions noted in earlier published reports. The Bureau of Drugs/FDA is currently preparing a report on serious morbidity and mortality associated with diet pills containing PPA, caffeine, and ephedrine, singly or in combination with each other (Kawazu HE: Personal Communications. FDA, February 1982). The discrepancy in the severity of reactions in the FDA report and the current study suggests many questions. The incidence of such reactions, their mechanisms of action and the true hazard to the community from such products remains to be addressed.

The popularity of OTC diet aids will likely continue to produce significant numbers of ingestions, both accidental and intentional. The results of this study indicate the majority of overdoses involving OTC diet aids will not be serious and may only require decontamination of the digestive tract and supportive care. We recommend that emesis be induced with reported ingestions of diet aids involving more than 8-10 mg of PPA in children. Deliberate ingestions by adults require careful consideration of the history of ingestion, the agents involved, and the intent of the victim. In most cases, emesis should be induced in all adult poisonings unless there is strong evidence not to. In children a dose of 8-10 mg/kg would be expected to produce only mild symptoms; however, the impact and trauma of forced emesis is considered less hazardous and preferable to allowing a victim to develop even mild symptoms. The use of this dose as a cut-off for the induction of emesis is consistent with our clinical impression that amounts of PPA below this quantity are well tolerated and are not expected to result in any more serious side effects. Obviously, if the history of ingestion cannot reliably be ascertained treatment should be performed. Physicians and poison control centers should recognize that these agents can produce life-threatening cardiac arrhythmias, hypertension, and other serious effects.

The challenge to pharmacists and physicians is to educate the consuming public to the safety and proper use of these and other substances for weight reduction. Treatment of serious adverse reactions or overdosage with OTC diet aids will continue to be a clinical problem as long as the public demand for this method of weight control remains constant.

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Dr. **Silverman**. Thank you, Dr. Winick. The next colleague to contribute is Dr. Noble from California, and from the University of California Hospital in San Francisco. Dr. Noble?

STATEMENT OF RUDOLF NOBLE

Dr. **Noble**. My name is Dr. Rudolf Noble. I hold both an M.D. degree and a doctorate in organic chemistry. Currently I am a clinical instructor in medicine at the University of California Hospital in San Francisco and I am director of the Cathedral Hill Obesity Clinic in the same city.

I have with me written testimony that I have asked to be entered into the record.

However, these are the important points of that testimony.

I have recently conducted a study of both the medical and psychological safety of phenylpropanolamine. This double blind study involved 216 patients and is part of a four-city, 864 on-going patient study. We have analyzed the medical data on my part of the study, that is to say, the 216 patients, and I can report to you that we found no significant changes in blood pressure or pulse rate whether the patients took a time-release 75 milligram dose of PPA or took a 25 milligram of PPA three times a day, as compared to the placebo group.

In addition, the psychological profile that we conducted on these patients indicated that PPA had no significant effect on mood.

As I wrote in a publication in the June 1982 issue of Lancet—and here I'd like to mention that that is not such a bad medical journal, Dr. Ramey—anyway, as I published in that journal before doing the study, in the past 2 years I have done three large studies in our obesity clinic involving more than 400 obese patients on the effect, over a period of 12 weeks, of 3 different dose forms of PPA.

Our results confirmed, even before my latest study that I just told you about, that PPA does not cause a significant increase in blood pressure, even in doses up to 150 milligrams.

In addition, I studied 60 patients who were given either PPA or an appetite-curbing medication available only by prescription. The weight loss was the same in both groups.

In my view, from my studies, PPA is a safe and effective over-the-counter appetite suppressant for the millions of people in this country who want to lose weight. Thank you very much.

[The prepared statement of Dr. Noble follows:]

Prepared Statement of Rudolf E. Noble, M.D., Ph. D., Director of Cathedral Hill Obesity Clinic, San Francisco, Calif.

Good morning. My name is Dr. Rudolf Noble. I hold a Doctorate in Organic Chemistry from the University of Colorado at Boulder and an M.D. degree from Western Reserve University.

I have been a Fulbright Post-Doctoral Research Fellow at the University of Heidelberg in Germany; a Research Fellow in Medicine at Western Reserve University and at the University of California Hospital in San Francisco, where I did my internship in medicine. I did my residency in medicine at Stanford Hospital.

Currently, I am clinical instructor in medicine at the University of California Hospital in San Francisco and director of the Cathedral Hill Obesity Clinic in the same city.

After the FDA Advisory Review Panel in 1979 pronounced phenylpropanolamine (PPA) to be both safe and effective, there have been sporadic reports throwing some doubt on that finding. Certainly, as director of the Cathedral Hill Obesity Clinic, I am very concerned with the safety and effectiveness of OTC drugs used as appetite suppressants. I am often asked about these medicaments by patients and I might be held liable for any given advice. Accordingly, I and others have been conducting new studies testing the safety of PPA.

In a significant, large-scale study I have recently conducted, we looked at 216 patients for both the medical and psychological safety of PPA at different dose levels compared with a placebo. Of these 216, 36 were of normal weight; 72 were 15–30 percent overweight; 72 were 31–45 percent overweight and 36 were more than 46 percent (or severely) overweight. The study has just been completed.

Patients were studied during a 12-hour period. Patients took a 75 mg time-release dose at approximately 8 A.M. and a placebo at approximately noon and 4 P.M. A second group took 25 mg at those times. A third group received a placebo at those three times. Patients were checked for blood pressure and pulse rate (both standing and lying down) on administration of the drug and at one-half hour, 1 hour, 2 hours, 4 hours, 4½ hours, 6 hours, 8 hours, 8½ hours, 10 hours and 12 hours afterwards. In addition, clinical measures of subjective emotional states were obtained using self-administered standardized mood-scales at each of the 11 measurement intervals.

In analyzing the clinical data, I can report to you that PPA at the 75 mg dose level causes no significant change in blood pressure or pulse rate. An analysis of the psychological mood-scale data also showed no significant changes in emotional state.

There was an incident that you should know about. One patient went home and later called in to report that she was hallucinating. Under our emergency procedures, we broke the seal on the medication she had been taking, only to discover that at each medication time that day, she had been taking the placebo.

This study is one phase of a four-phase study. The same study is being replicated for 216 patient groups in Seattle, New York and Boston.

What do I think about PPA? Let me summarize what I wrote in a letter that was published in June 1982 in *The Lancet* prior to undertaking the study I've just described. (Exhibit A) To quote parts of that letter: "In the past two years, I have done three large studies in our obesity clinic in San Francisco of the effects of three dosage forms of PPA. More than 400 obese patients were studied.

"Data were gathered on a twelve-week, double-blind, placebo controlled study of 50 mg PPA three times daily (twice the recommended dose for weight loss); a double-blind placebo controlled study of 50 mg PPA combined with 200 mg caffeine in controlled-release form; and a single-blind trial of 75 mg PPA in controlled-release form.

"Our results confirm that PPA does not cause a significant increase in blood pressure even when the amount ingested (150 mg/day) is substantially higher than the recommended 75 mg dose. There was, on the contrary, a reduction in blood pressure as the studies progressed."

My acute and chronic studies subsequently show, ladies and gentlemen, that PPA is a safe and effective appetite suppressant for millions of people in this country who want or need to lose weight.

Thank you.

Noble, R. E., Exhibit

A. Phenylpropanolamine and Blood Pressure, The Lancet, June 19, 1982

PHENYLPROPANOLAMINE AND BLOOD PRESSURE

SIR,—Although phenylpropanolamine (PPA) has been safely used in the U.S.A. for over forty years as a nasal decongestant, your April 10 editorial raised the possibility that PPA in weight control preparations could produce increased blood pressure.

In the past two years, I have done three large studies in our obesity clinic in San Francisco of the effects of three dosage forms of PPA. More than 400 obese patients were studied. The results will be published elsewhere.

Data were gathered on a twelve-week, double-blind, placebo controlled study of 50 mg PPA three times daily (twice the recommended dose for weight loss); a double-blind, placebo controlled study of 50 mg PPA combined with 200 mg caffeine in controlled-release form; and a single-blind trial of 75 mg PPA in controlled-release form.

All three dosages caused no significant increase in blood pressure in more than 400 patients. 2 patients experienced noteworthy rises in blood pressure after treatment with 75 mg PPA, but these increases were felt not to be drug related.

The mean pooled systolic and diastolic blood pressure in the 50 mg × 3 PPA/placebo study are shown in the figure.

Our results confirm that PPA does not cause a significant increase in blood pressure even when the amount ingested (150 mg/day) is substantially higher than the recommended 75 mg dose. There was, on the contrary, a reduction in blood pressure as the studies progressed.

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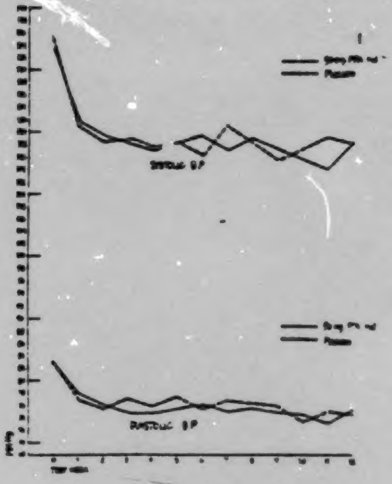
RUDOLF E. NOBLE



Mean systolic and diastolic blood pressure.

Ms. **Oakar**. Thank you, Doctor.

Dr. **Silverman**. Thank you, Dr. Noble. Next we will hear from Dr. Conte. Dr. Conte is an internist who practices in Beaver, Pa., and specializes in the treatment of the obese. Dr. Conte?

STATEMENT OF DR. ANTHONY CONTE

Dr. **Conte**. My name is Dr. Anthony Conte. I am a bariatrician, who is a physician who specializes in the medical management of weight control. I have been in private practice for more than 20 years in Beaver, Pa., where I direct a clinic for obese patients and I'm proud to say that I treat patients, not scales.

I have brought with me written testimony that I request be entered into the record.

Ms. **Oakar**. Without objection.

Dr. **Conte**. I wanted to share with you the important points of that testimony. Over the past 7 years I have prescribed or recommended phenylpropanolamine to approximately 7,000 obese patients, including patients with elevated blood pressure. I can tell you that I've never observed any adverse side reactions in these patients.

On the contrary, I have found PPA to be a valuable adjunct in the treatment of obesity. In published studies that my colleague and I have done comparing the safety and effectiveness of PPA against a placebo and against appetite suppressants available by prescriptions only, I have found PPA to be equally effective as prescription drugs and far more effective than placebos in helping patients lose weight.

I have not found any significant side effects, changes in blood pressure, during and after several months of use. In short, phenylpropanolamine is, in my view, a safe and effective product which, when used as directed, offers help to the 80 million Americans who need to lose weight for the sake of their health and well-being. Thank you.

[The prepared statement of Dr. Conte follows:]

PREPARED STATEMENT OF ANTHONY CONTE, M.D., BARIATRICIAN, BEAVER, PA.

Good morning. My name is Anthony Conte. I am a physician with a specialty in bariatrics—the treatment of obesity. I have been in private practice for more than 20 years in Beaver, Pennsylvania, where I direct a clinic for obsese patients, and am an attending physician at the Medical Center of Beaver County. I received my MD degree from the University of Buffalo School of Medicine in Buffalo, New York in 1950. From 1957-64, I was the Director of Anesthesiology at both Beaver Valley General Hospital in New Brighton, Pennsylvania, and Providence Hospital, in Beaver Falls, Pennsylvania. I was invited to participate in the 1969 White House Conference on Nutrition. I am currently a nutrition consultant for the University of Pittsburgh Department of Athletics.

Over the past 20 years, I have treated more than 25,000 patients suffering from obesity—a health-threatening condition affecting 80 million people in this country. I have observed patients who are desperately trying to lose weight, trying to change eating habits that had been followed for a lifetime. And, I have seen patients leave my office 20 or more pounds lighter than when they first consulted with me.

In my obesity clinics, my treatment method varies with each patient. But one of the more consistently effective treatments, which offers help to a broad segment of obese patients, has been the use of phenylpropanolamine to suppress the appetite and make it easier for patients to cut down their caloric intake. Over the past seven years, I have prescribed or recommended PPA to approximately 7,000 patients, including patients with elevated blood pressure. I can tell you that I have never observed any adverse side effects in these patients. I have found PPA to be a valuable adjunct in treating obesity.

Before any patient begins treatment with me, he or she undergoes a complete physical examination, a series of blood tests, a nutritional evaluation, an electrocardiogram, and an evaluation of the status of the cardiac, kidney and liver systems. In follow-up visits, which take place at least once a month, the patient's weight, blood pressure and pulse are checked.

Part of my professional practice also includes carrying out scientifically controlled studies to measure the effectiveness of various methods in treating obesity. I have reported my findings at meetings and symposia of the American Society of Bariatric Physicians and the International Academy of Preventive Medicine. I have published papers in the International Journal of Obesity and in Obesity and Bariatric Medicine, the journal of the American Society of Bariatric Physicians. I have also carried out research studies for various pharmaceutical companies, including A. H. Robins, Sandoz, Smith, Kline and French, and Thompson Medical.

I'd like to review some key findings of some of my research that relate to the subject of today's hearing.

In an article published in 1982 in the International Journal of Obesity, I reported with other investigators on research we carried out which studied the use of a phenylpropanolamine-caffeine combination in overweight patients. 201 patients were studied to compare the safety and efficacy of PPA against a placebo and against mazindol and diethylpropion, which are both appetite suppressants available by prescription only.

Over a period of 6 weeks, patients taking PPA lost significantly more weight than those taking a placebo: 4.64 pounds compared to 2.07 pounds. And, when we compared PPA to mazindol and diethylpropion, we found PPA to be equal to those products in helping patients lose weight. The effectiveness of PPA was clearly demonstrated.

Patients in this study were required to visit the physician every two weeks to be weighed. At each visit, blood pressure and pulse were recorded, and patients were asked about any side effects or adverse reactions. They also had to return any unused medication. We found that patients taking PPA had fewer side effects than patients on mazindol or diethylpropion. In fact, in the PPA versus placebo group, two patients taking the placebo reported side effects: dry mouth, diuresis and itching. These reactions are often observed in people who are starting to diet and change their eating habits.

In another study, I compared phenylpropanolamine with diethylpropion, an appetite suppressant available by prescription only. In a group of 48 patients, no significant differences were seen in the amount of weight lost by patients taking PPA as compared to diethylpropion. And, there were no clinical deviations in blood pressure or pulse in either group.

My interpretation of the findings of these and other studies is that phenylpropanolamine is a safe and effective product which, when used as directed, offers help to the 80 million Americans who need to lose weight for the sake of their health and well-being. I intend to continue recommending it to my patients.

I am submitting my comments, and a copy of the study I referred to, to be entered into the record. Thank you.

Conte, A., Exhibit

A. Altschuler, S., Conte, A., Sebok, M., Marlin, R. L., and Winick, C., Three controlled trials of weight loss with phenylpropanolamine, International Journal of Obesity (1982) 6, 549-556

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Three controlled trials of weight loss with phenylpropanolamine

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Summary

A multisite double-blind study was designed to determine the effectiveness of a phenylpropanolamine-caffeine combination in achieving weight loss. Two-hundred and one obese adult patients were divided into three separate groups in which phenylpropanolamine/caffeine was compared with either placebo (6 weeks), mazindol (6 weeks), or diethylpropion (8 weeks). In these clinical trials, phenylpropanolamine/caffeine proved to be as effective as mazindol and diethylpropion and significantly more effective than placebo in achieving weight loss. Overall, phenylpropanolamine/caffeine had fewer side effects than mazindol and diethylpropion. Its use as an effective anorectic agent in the treatment of obesity is reviewed.

Introduction

The substantial professional and consumer concern about obesity in America has led to a growing interest in appetite suppressants as substances for assisting people to lose weight. This is a report on an integrated program of three controlled studies on phenylpropanolamine/caffeine as an appetite suppressant.

Phenylpropanolamine is a sympathomimetic drug which is a synthetic derivative of ephedrine. It is a β-phenethylamine with a methyl substitute on the 2 carbon and a hydroxyl group on the beta carbon. The latter substitution generally decreases CNS activity[3]. In rats[4], and in monkeys[5], phenylpropanolamine curbs food intake without overt signs of change in activity level. Caffeine has no appetite suppression effect but is included because many patients on weight reduction regimens experience fatigue and lassitude, which the caffeine helps to counteract.

In the current double-blind studies conducted with overweight adults, there was a 6-week comparison of a placebo (Study I), a 6-week comparison against mazindol (Study II), and an 8-week comparison against diethylpropion (Study III).

Subjects and methods

Subjects

All study patients were between 18 and 65 yr old and from 12 to 45 percent overweight, as determined from the Metropolitan Life Insurance tables. (*Statistical Bulletin*, 40, 1, 1959 & 47, 1, 1966).

The examining physician measured the patient's height to the nearest inch and weight to the nearest pound. The physician then evaluated each patient's frame as either small, medium, or large. Taking the midpoint of the desirable weight for the patient's height and frame size from the Metropolitam Life Insurance Company tables, the degree of overweight in per cent was determined by the formula:

$$\frac{\text{actual weight} - \text{desirable weight}}{\text{desirable weight}} \text{ X } 100$$

No patient had any clinical disease or surgical condition which might interfere with the medication; no patient was pregnant or lactating, or had participated in any weight reduction program for at least 3 weeks preceding the study. Informed consent was obtained in writing from all patients. The patients, recruited from the physician's private practice, were told about the procedures and goals of the study.

At the first session, a history of each patient was taken and a physical examination conducted. Patients were required to appear every 2 weeks thereafter, to be interviewed and weighed by the physician. At each visit, blood pressure and pulse were measured and the patients were asked to report any side effects or adverse reactions and return all unused medication. All the study data collection were carried out with similar case report forms.

If a patient reported any side effects or reactions, the physician obtained full details, evaluated their significance, and recorded them on the patient's record. The physician also recorded the absence of such effects or reactions, when appropriate.

In each of the three studies, patients were randomly assigned to one of two groups, which were essentially homogenous in terms of entrance criteria. Each experimental group received either a placebo or phenylpropanolamine 37.5 mg, 140 mg caffeine (sustained release)* b.i.d. (Study I), mazindol 2 mg or phenylpropanolamine 50 mg and 200 mg caffeine (sustained release)** once a day (Study II), or diethylpropion 25 mg or phenylpropanolamine 25 mg, 100 mg caffeine*** t.i.d. (Study III). The substances being compared were in identically-appearing capsules. In each of the three studies, the amount of phenylpropanolamine contained in the capsule was different, so that the frequency of ingestion

**Available commercially as Prolamine; **Available commercially as Dexatrim; ***Available commercially as Appedrine; all products distributed by Thompson Medical Company, Inc., New York, NY 10022.*

was different, as noted above. Patients in Study I were not required to follow a specific diet but were encouraged to follow sound nutritional principles. However, all patients in Studies II and III were provided with a balanced 1250 calorie (5.23 MJ) diet, along with instructions on its use. All patients were seen every other week and all data were entered on similar case report forms.

Procedures

Study I. Study I followed a double-blind comparison of a placebo (lactose) against 37.5 mg phenylpropanolamine with 140 mg of caffeine, in a sustained action capsule. The patients took either test medication daily at 1000 h and 1600 h for 6 weeks and were given no specific diet. There were 72 patients. Mean initial weight for the medicated patients was 161 lb (73 kg) with a range from 131 to 203 lb (60-92 kg). Mean initial weight for the placebo patients was 162 lb (74 kg), with a range from 118 to 205 lb (54-93 kg). The medicated group included six males and 22 females; there were nine males and 19 females in the placebo group.

Study II. Study II consisted of a comparison of 50 mg of phenylpropanolamine with 200 mg caffeine, against 2 mg of mazindol, an imadazoisoindole anorexiant in the Drug Enforcement Administration's Schedule III, which has been found to be superior to placebo as an appetite suppressant[3,17]. The patients took either medication once daily at 1000 h, for 6 weeks and were given a 1250 calorie (5.23 MJ) nutritionally balanced diet. There were 67 patients entered (58 female, nine male). Mean initial weight for the mazindol patients was 169 lb (74 kg), with a range from 122 to 240 lb (55-109 kg). Mean initial weight for the phenylpropanolamine patients was 170 lb (77 kg), with a range from 118 to 240 lb (54-109 kg). The mazindol group included five males and 23 females; there were three males and 24 females in the phenylpropanolamine group.

Study III. Study III compared 25 mg of phenylpropanolamine with 100 mg caffeine and multi-vitamins, against diethylpropion, a phenethylamine anorexiant in the Drug Enforcement Administration's Schedule III, which was found to be clinically effective in achieving weight reduction[15]. Either medication was taken three times daily, 30 min before each meal, over 8 weeks, with a 1250 calorie (5.23 MJ) nutritionally balanced diet. There were 62 patients (59 female, three male). Mean initial weight for the phenylpropanolamine/caffeine/vitamins group was 161 lb (73 kg), with a range from 120 to 219 lb (55-100 kg). Mean initial weight for the diethylpropion group was 160 lb (73 kg), with a range from 129 to 196 lb (59-89 kg). The phenylpropanolamine group included one male and 24 females; there was one male and 22 females in the diethylpropion group. *(Numbers within groups signify patients who completed the study).*

Results

Study I

The mean and standard deviation of the cumulative weight loss occurring at weeks 2, 4, and 6 are set forth in Table 1. Phenylpropanolamine was consistently associated with more weight loss than the placebo; the difference, as measured by Student's *t*-test and analysis of variance, was not statistically signifi-

Table 1. Comparison of weight loss achieved by phenylpropanolamine vs placebo, mazindol and diethylpropion at 2-week intervals

Medication	Change in body weight from baseline															
	Baseline to 2 weeks				Baseline to 4 weeks				Baseline to 6 weeks				Baseline to 8 weeks			
Study I. Phenylpropanolamine vs placebo																
	lb	kg	s.e. ±	kg	lb	kg	s.e. ±	kg	lb	kg	s.e. ±	kg				
Phenylpropanolamine/caffeine (*n* = 28)	–3.07	1.39	0.49	0.22	–3.71	1.68	0.60	0.27	–4.64	2.10	0.72	0.32				
Placebo (*n* = 28)	–1.96	0.89	0.40	0.18	–1.88	0.76	0.62	0.28	–2.07	0.94	0.69	0.31				
Study II. Phenylpropanolamine vs mazindol																
	lb	kg	s.e. ±	kg	lb	kg	s.e. ±	kg	lb	kg	s.e. ±	kg				
Phenylpropanolamine/caffeine (*n* = 27)	–4.22	1.91	0.68	0.30	–5.7	2.60	0.73	0.33	–8.11	3.68	1.02	0.46				
Mazindol (*n* = 28)	–4.50	2.04	0.57	0.25	–6.53	2.96	0.66	0.30	–9.00	4.08	0.79	0.35				
Study III. Phenylpropanolamine vs diethylpropion																
	lb	kg	s.e. ±	kg	lb	kg	s.e. ±	kg	lb	kg	s.e. ±	kg	lb	kg	s.e. ±	kg
Phenylpropanolamine/caffeine (*n* = 25)	–3.40	1.54	0.47	0.21	–4.92	2.23	0.60	0.27	–5.67	2.57	0.80	0.36	–6.84	3.10	0.85	0.38
Diethylpropion (*n* = 23)	–4.04	1.83	0.61	0.27	–5.61	2.54	0.86	0.39	–6.61	3.00	1.17	0.53	7.96	3.61	1.44	0.65

cant at week 2 but was significant at week 4 ($P < 0.02$) and week 6 ($P < 0.01$). The approximately 2:1 ratio of weight loss achieved by patients on phenylpropanolamine as compared to those on placebo, is consistent with the results of a review of pooled studies involving 7000 patients who were taking prescription anorectic drugs compared to placebo, over a variety of time intervals[13].

Four patients on phenylpropanolamine reported adverse reactions: dry mouth, diuresis, diarrhea, and constipation. One placebo-treated patient experienced dry mouth and diuresis and another cited itching. The reactions, which occurred only during the first 2 weeks, are not uncommon in persons starting weight reduction programs and changing their food intake patterns. Blood pressure and pulse readings were taken at each visit. The means for each are reported in Table 2.

Of the eight patients using phenylpropanolamine who dropped out of the study, five could not keep appointments, one had no transportation, another experienced nausea, and one was terminated by his family physician. These reasons were determined, in this and the other studies, by follow-up calls to the patients. Of the eight patients on placebo who dropped out, five could not keep appointments, one experienced nausea, another had no transportation, and one was terminated by her family physician.

Table 2. Diastolic and systolic pressure and pulse at beginning and end of study

	Diastolic (mmHg)		Systolic (mmHg)		Pulse (beats/min)	
	beginning	end	beginning	end	beginning	end
Study I (6 week evaluation)						
Phenylpropanolamine/caffeine b.i.d. (n =28)						
mean	78.9	78.1	124.4	124.4	73.4	72.9
range	70-90	65-90	110-150	110-150	68-82	68-82
Placebo b.i.d. (n = 28)						
mean	84.3	82.2	128.3	127.7	74.2	73.5
range	65-90	70-100	110-150	110-150	64-88	70-88
StudyII (6 week evaluation)						
Mazindol o.d. (n = 28)						
mean	79.3	75.9	120.6	118.2	76.4	75.2
range	58-94	54-88	108-146	102-138	64-90	66-96
Phenylpropanolamine/caffeine b.i.d. (n 27)						
mean	76.6	76.3	115.6	117.4	75.3	74.3
range	60-90	62-86	90-142	96-150	60-90	60-86
Study III (8 week evaluation)						
Diethylpropion t.i.d. (n = 23)						
mean	71.4	72.0	111.2	113.5	77.2	78.3
range	60-80	60-82	94-130	100-140	62-88	72-100
Phenylpropanolamine/caffeine/vitamins (n = 25)						
mean	69.9	70.1	110.8	112.8	78.1	78.8
range	54-82	58-88	98-126	96-140	60-100	68-86

Study II.

The mean and standard deviation of the cumulative weight loss occurring at weeks 2, 4 and 6 are summarized in Table 1. At each measuring point, as measred by Student's *t*-test and analysis of variance, there was no significant difference between phenylpropanolamine and mazindol in terms of weight loss.

None of the phenylpropanolamine patients reported any side effects but seven mazindol patients did so ($P < 0.05$). These included: constipation (2), dry mouth (2), nervousness (1), hot flushes (1), lightheadedness (1). Blood pressure and pulse readings were taken at each visit and the means are reported in Table 2.

Six patients treated with phenylpropanolamine gave no specific reason for dropping out, one did because he was not losing weight. Of five patients treated with mazindol who dropped out, two gave no reason, one became irritable, another had a dispute with her husband, and one was not losing weight.

Study III

Table 1 sets forth the mean and standard deviation of the cumulative weight loss of the phenylpropanolamine and diethylpropion group, at weeks 2, 4, 6, and 8. There was no significant difference between the two groups, at any point of measurement, as measured by Student's *t*-test and analysis of variance.

Five patients treated with phenylpropanolamine experienced side effects: dry mouth (2), headache (1), nervousness (1) and cramps (1). Seven patients treated with diethylpropion experienced: headache (2), nervousness (2), cramps (1), insomnia (1), and too much energy (1). Blood pressure and pulse measurements were taken at each visit and the mean cases are reported in Table 2.

Six patients treated with phenylpropanolamine dropped out, because of: schedule conflicts (2), lightheadedness (1), moving away (1), discouragement (1) and a broken leg (1). Eight patients treated with diethylpropion dropped out, for various reasons: couldn't keep appointments (2), not effective enough (2), schedule conflicts (1), nervousness (1), stomach cramps (1) and no specific reason (1).

Discussion

A number of earlier studies have suggested the possible utility of phenylpropanolamine as an adjunct to the treatment of obesity[9,12]. Phenylpropanolamine's appetite suppresant effect is well established and recognized by the US Pharmocopeia Convention[16]. Its use for this purpose has assumed additional relevance because of the growing concern over the use of amphetamines in the treatment of obesity. Amphetamines have actually been barred for such purposes in England (1968), Sweden (1970) and Canada (1972). Phenylpropanolamine's abuse potential is practically non-existent[7], as is its tolerance potential[18]. A previous report raised questions about the safety of phenylpropanolamine in achieving weight loss[11]. This report, however, was based on experience utilizing dosages larger than those employed in the United States. However, in a study of 37 adults, it was found that phenylpropanolamine (25 mg) by itself in combination with caffeine (100 mg) had no significant effect on either systolic or diastolic blood pressure measured at intervals over a 4-h period[14]. As set forth in Table 2, phenylpropanolamine has minimal negative cardiovascular impact.

In one double-blind crossover study, phenylpropanolamine reduced body weight significantly more than a placebo, without noticeable stimulatory side effects[10].

Another previous double-blind study, in which the patients had been given a nutritionally balanced diet had found phenylpropanolamine to be superior, to a statistically significant degree, to a placebo in achieving weight loss[6]. Similar results were achieved in the current investigation (Study I), in which the patients were advised to use good nutritional judgment, but were not given a formal diet. It was felt that not providing the patients with a specific diet would add an additional dimension to the investigation.

The current study also implements the suggestion of an experienced bariatric physician that clinical assessments of anorectic drugs employ more than one dosage level[1]. In the current study, three different dosage levels were used, as well as different settings: a general hospital, Veterans Administration hospital, and a private office. The hospitals are located in a large city (Philadelphia), and the private practice in a suburban community in the same state.

On the basis of previous findings and of the current study, phenylpropanolamine would appear to merit consideration as an anorectic agent of choice based on its efficacy, safety, and lack of abuse potential.

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Ms. Oakar. Thank you, Dr. Conte.

Dr. Silverman. Next is Dr. Marianne Sebok, internist, from Philadelphia, and associated with the Albert Einstein Hospital in that city. Dr. Sebok.

STATEMENT OF DR. MARIANNE SEBOK

Dr. Sebok. Thank you. My name is Dr. Marianne Sebok. I am a physician working in internal medicine. I have been in the practice of medicine for 33 years and I am now in private practice in Philadelphia, connected with the Albert Einstein Memorial Hospital, Frankford Hospital, and John F. Kennedy Hospital. I have a written testimony that I submitted to the committee.

I would like to give you, now, some highlights of this record.

Obesity is a major health problem in the United States, affecting some 80 million Americans, who are approximately 35 percent of the population. It can be a potential killer. Weight is usually a signficant predicter of cardiovascular disease in men and women, even when statistical adjustments are made for cigarette smoking, age, and hypertension.

I have performed, as you can see here, double blind clinical studies on over 200 people who were in good health, to test the safety and efficacy of phenylpropanolamine, otherwise known as PPA.

Patients who took phenylpropanolamine lost twice as much weight as those who were only on placebo. I have not observed, personally, any significant side effects from the use of PPA or phenylpropanolamine.

In my opinion, phenylpropanolamine is safe and effective, if used as prescribed, not only as an appetite suppressant, but also as a nasal decongestant or cold medicine. And this was used, it was used as this for the last 50 years.

Thank you.

[The prepared statement of Dr. Sebok follows:]

PREPARED STATEMENT OF MARIANNE SEBOK, M.D., PHYSICIAN, AFFILIATED WITH J. F. KENNEDY MEMORIAL HOSPITAL, FRANKFORD HOSPITAL, AND ALBERT EINSTEIN MEMORIAL CENTER, PHILADELPHIA, PA.

Good morning. My name is Dr. Marianne Sebok. I have been practicing medicine for 33 years—beginning first in Hungary and then in Switzerland. In 1960, I came to the United States to begin a four-year residency at the Albert Einstein Medical Center in Philadelphia, specializing in haemotology and chemotherapy. In 1965, I was appointed staff physician at J. F. Kennedy Memorial Hospital in Philadelphia. I continued to practice there until 1973 when I left to start my own practice in Philadelphia. Currently I am affiliated with the J. F. Kennedy Memorial Hospital, Frankford Hospital and Albert Einstein Memorial Center, all in Philadelphia.

My purpose in speaking to you today in twofold: First, to alert you to the staggering mortality rates associated with obesity, and second, to point out the safety and effectiveness associated with phenylpropanolamine—or PPA—as an appetite suppressant to achieve weight loss.

Phenylpropanolamine is a far better alternative in weight loss than crash diets, fads and liquid protein supplements. Phenylpropanolamine is a safe and effective appetite suppressant which can help overweight people lose weight. The only way to lose weight safely and effectively is to reduce the number of calories consumed. PPA can be used as an appetite suppressant while obese people learn new eating habits.

When I use the term obesity I'm referring to people 10 percent or more overweight. Government data puts that figure at 80 million Americans—approximately 35 percent of the total population.

Complicating diseases—coronary heart disease, cancer, diabetes, digestive diseases and cerebral vascular disease—profoundly increase the chance of early death when a person is obese.

In a study by Lew and Garfinkel, a base of 750,000 men and women was used to calculate mortality rates as related to obesity. The recently completed Framingham Heart study also found a distinct relationship between overweight and mortality rates. Let me point out some highlights from these two studies. (Exhibit A)

Weight is a significant predictor to total cardiovascular diseases in both men and women, even when statistical adjustments are made for cigarette smoking, hypertension, age, left ventricular hypertrophy and serum levels of cholesterol and glucose.

Weight is one of the best predictors of myocardial infarction, stroke and all type of cardiovascular death in women, ranking only behind age and blood pressure.

Overweight females in their 50s, 60s and 70s are one and two-thirds more likely to die of cancer.

Digestive diseases are four times more likely to result in death in overweight men and two times more likely in overweight women.

Obese diabetic women in their forties are almost 25 times more likely to die than if they were at normal weight.

For both sexes, people are almost twice as likely to die of complicating diseases if they are obese.

Mortality resulting from complications of obesity is at its highest among people in their 40s and 50s.

Obviously, for 35 percent of the American population, losing weight is a matter of life and death.

Phenylpropanolamine is purchased by 10 million American each year for help in dieting. In my research with PPA as an appetite suppressant, I studied 134 overweight men and women in three separate double-blind trails.

In the first, 54 patients were divided into two groups. One group received an appetite suppressant that contained 50 mg of phenylpropanolamine, and the other group received a placebo. Patients were required to follow a 1,250 calorie nutritionally balanced diet consisting of high protein, low fat, and restricted amount of carbohydrates. Patients took their test medication twice a day for six weeks.

Background information on each patient was collected including physical condition, body weight, frame, ideal weight, percent overweight, sitting blood pressure and pulse. At weeks two, four and six, the body weight, sitting blood pressure and pulse were rechecked. Patients were also questioned about adverse reaction.

After six weeks of evaluation, there was a statistically significant weight loss in the medicated group as compared to the placebo at a .05 level of confidence.

The second study involved 72 obese adults. The study procedure was identical to the first study, except that patients were not restricted to a 1,250 calorie diet.

Fifty-six patients completed the study. The PPA group lost a significant amount of weight as compared to the placebo group at a .01 level of confidence.

Most important, however, is that throughout the study no clinically significant variations in sitting blood pressure or pulse were observed.

In the final study, 70 patients were selected and 49 completed the study. The only side effects reported were minor, subjective symptoms that appeared in both the medicated and the placebo groups. These occurred among some people in both groups and were considered mild and did not persist.

This six-week evaluation revealed that of those patients taking Prolamine (35 mg phenylpropanolamine plus 140 mg caffeine B.I.D.) over a six-week period, 35 percent lost eight pounds or more and 22 percent lost six pounds or more. Of those taking a placebo, only nine percent lost eight pounds or more, and 22 percent lost six pounds or more. Of those taking phenylpropanolamine, 35 percent lost five percent or more of their initial body weight, while only four percent of the patients on placebo lost 5 percent of their initial body weight.

No significant changes in either blood pressure or pulse measurements were indicated during the test periods in comparison with the baseline measurement.

Sebok, M., Exhibit

A. Influence of Obesity on Mortality Rates of Men and Women in Disease and Non Disease States

INFLUENCE OF OBESITY ON MORTALITY RATES OF MEN AND WOMEN IN VARIOUS DISEASE AND NON DISEASE STATES

MORTALITY RATIOS FROM CORONARY HEART DISEASE BY AGE AND SEX IN RELATIONSHIP TO DEATH RATES OF THOSE 90-100% OF AVERAGE WEIGHT

		WEIGHT INDEX						
AGE GROUP	SEX	<080	080-089	090-109	110-119	120-129	130-139	140+
30-39	M	0.54*	0.79	1.00	1.46	2.03	1.49	NSD
	F	NSD	0.88	1.00	2.27*	2.29*	NSD	NSD
40-49	M	0.60	0.74	1.00	1.34	1.67	1.93	1.98
	F	1.00	0.65	1.00	1.59	2.71	2.71	3.61
50-59	M	0.77	0.86	1.00	1.28	1.42	1.76	2.16
	F	0.98	0.82	1.00	1.45	1.84	2.16	3.11
60-69	M	0.90	0.94	1.00	1.21	1.22	1.34	2.18
	F	0.93	0.89	1.00	1.30	1.43	1.65	1.88
70-79	M	1.17	1.02	1.00	1.09	1.22	1.52	1.41
	F	1.06	0.97	1.00	1.09	1.25	1.29	1.41
80-89	M	1.32	1.00	1.00	1.12	0.81	0.61*	1.43*
	F	1.11	1.04	1.00	0.97	0.92	0.61	1.23

NSD, not sufficient data (less than 5 observed deaths).
*Mortality ratio based on only 5-9 observed deaths.

Coronary heart disease was particularly high among women in their forties and fifties; in the weight index category 140 plus female mortality from this cause was from three to three and a half times higher than that in the 90-109 weight index category. Among men in the same age range corresponding coronary disease mortality was only about two times higher. At ages under 70 coronary disease mortality appears to be somewhat lower among underweights than among those of about average weight in both sexes.

MORTALITY RATIOS FROM CANCER OF ALL SITES BY AGE AND SEX IN RELATION TO DEATH RATES OF THOSE 90-109% OF AVERAGE WEIGHT

		Weight Index						
Age Group	Sex	<080	080-089	090-109	110-119	120-129	130-139	140+
30-39	M	1.93*	1.36	1.00	0.90	NSD	NSD	NSD
	F	0.85	0.84	1.00	1.47	0.93	0.92*	1.16
40-49	M	1.49	1.21	1.00	0.96	1.10	1.19	1.31
	F	0.95	0.94	1.00	0.97	1.14	1.19	1.37
50-59	M	1.46	1.13	1.00	1.08	1.13	1.09	1.52
	F	1.00	0.92	1.00	1.14	1.16	1.12	1.67
60-69	M	1.76	1.12	1.00	1.00	1.05	1.17	1.13
	F	1.11	0.97	1.00	1.16	1.37	1.29	1.79
70-79	M	1.25	1.09	1.00	0.95	1.09	1.32	1.15
	F	0.72	0.31	1.00	0.99	1.01	1.32	1.59
80-89	M	1.19	0.79	1.00	0.66	1.11	NSD	NSD
	F	0.80	0.99	1.00	1.22	1.35	1.98	NSD

Significantly higher mortality from cancer among female overweights was evident only in the weight index category 140 plus, in the fifties, sixties and seventies of age; specifically it was about one and two-thirds higher than that in the average weight index category 90-109. Excess mortality from cancer among male overweights was less pronounced than among women overweights, being only about one third to one half higher in the weight index category 140-plus.

MORTALITY RATIO FROM DIABETES BY AGE AND SEX IN RELATION TO DEATH RATES OF THOSE 90-109° OF AVERAGE WEIGHT

		Weight Index						
Age Group	Sex	<080	080-089	090-109	110-119	120-129	130-139	140+
30-39	M	NSD	NSD	1.00*	NSD	NSD	NSD	NSD
	F	NSD	NSD	NSD	NSD	NSD	NSD	NSD
40-49	M	NSD	1.99	1.00	2.64	3.56*	NSD	NSD
	F	NSD	NSD	1.00	3.55	9.56	NSD	24.59
50-59	M	1.17*	0.90	1.00	1.71	2.88	5.35	7.06*
	F	1.00*	0.64	1.00	2.28	4.35	7.12	12.32
60-69	M	0.71*	0.64	1.00	1.33	2.87	2.07*	NSD
	F	0.60*	0.66	1.00	2.05	3.54	3.58	4.12
70-79	M	NSD	0.69	1.00	1.52	1.74	NSD	NSD
	F	0.55*	0.64	1.00	1.51	1.65	1.75*	4.40*
80-89	M	NSD	NSD	1.00	2.79	NSD	NSD	NSD
	F	NSD	NSD	1,00	1.02*	2.90	NSD	NSD

NSD. Not sufficient data (less than 5 observed deaths).
*Mortality ratio based on only 5-9 observed deaths.

Mortality from diabetes was reltively highest among women overweights in their forties and fifties; the excess mortality from diabetes diminished with advancing age among overweight women. Among men overweights at ages under 70 the excess mortality was distinctly lower than among women and did not vary as much by age. Note that the mortality ratio of a female in her forties at least 40% overweight is 24.59!

MORTALITY RATIOS FROM DIGESTIVE DISEASES BY AGE AND SEX IN RELATION TO DEATH OF THOSE 90-109% OF AVERAGE WEIGHT

Age Group	Sex	Weight Index <080	080-089	090-109	110-119	120-129	130-139	140+
30-39	M	NSD	1.77*	1.00	NSD	NSD	NSD	NSD
	F	NSD	1.58	1.00	NSD	NSD	NSD	NSD
40-49	M	0.91*	1.35	1.00	1.67	2.76	6.00	NSD
	F	2.07	0.98	1.00	1.27	NSD	NSD	3.81
50-59	M	1.51	1.38	1.00	1.20	2.10	3.23	5.11
	F	1.71	1.13	1.00	1.98	2.13	2.15*	NSD
60-69	M	1.65	1.09	1.00	1.65	1.45	1.80*	4.67*
	F	1.75	0.56	1.00	1.61	0.98*	1.86*	NSD
70-79	M	1.26*	1.22	1.00	1.52	1.14*	NSD	NSD
	F	0.96*	0.64	1.00	1.88	2.54	3,77	NSD
80-89	M	NSD	NSD	1.00	1.55*	NSD	NSD	NSD
	F	NSD	0.98*	1.00	1.08*	NSD	NSD	NSD

NSD. Not sufficient data (less than 5 observed deaths).
*Mortality ratio based on only 5-9 observed deaths.

The second highest relative mortality among overweights of both sexes was from digestive diseases. In the 140 plus weight index category the mortality from these diseases was four times that in the 90-109 weight index for males and two and a quarter times for females. Both male and female underweights in the below 80 weight index category recorded distinctly higher death rates, approximately one and a half times those in the 90-109 weight index.

SUMMARY

MORTALITY RATIOS FOR ALL AGES COMBINED IN RELATION TO THE DEATH RATE OF THOSE 90-109% OF AVERAGE WEIGHT

	7th Rev* ICD	Sex	Weight Index 080	080-089	090-109	110-119	120-129	130-139	140+
Total deaths		M	1.25	1.05	1.00	1.15	1.27	1.46	1.87
		F	1.19	0.96	1.00	1.17	1.29	1.46	1.89
Coronary heart disease	420	M	0.88	0.90	1.00	1.23	1.32	1.55	1.95
		F	1.01	0.89	1.00	1.23	1.39	1.54	2.07
Cancer, all sites	140-205	M	1.33	1.13	1.00	1.02	1.09	1.14	1.33
		F	0.96	0.92	1.00	1.10	1.19	1.23	1.55
Diabetes	260	M	0.88	0.84	1.00	1.65	2.56	3.51	5.19
		F	0.65	0.61	1.00	1.92	3.34	3.78	7.90
Digestive disease	540-542 570-578	M	1.39	1.28	1.00	1.45	1.88	2.89	3.99
	584-586	F	1.58	0.92	1.00	1.66	1.61	2.19	2.29
Cerebral vascular disease	330-334	M	1.21	1.09	1.00	1.15	1.17	1.54	2.27
		F	1.33	0.98	1.00	1.09	1.16	1.40	1.52

*International Classification of Diseases, 7th Revision

The mortality experienced in each weight index category from all causes of death and from each of five broad cause of death classes is shown above for all ages combined by sex. These causes were shown because they are the major causes of death or have been shown in other studi to be associated with overweight. By definition the mortality ratios in the 90-109 weight ind category are all 100%. It should be noted that the mortality ratios shown for other weight index categories have all been adjusted for time period and smoking class.

For males the optimal mortality weight index was 90-109; for females those with weight index 80-89 recorded death rates 4% lower than those in the 90-109 weight index category. In both sexes relative mortality was higher among those in the below 80 weight index category than in the 90-109 weight index. With increase in weight the mortality ratio among males rose to 115% for the 110-119 weight index category, 127% for the 120-129 weight index, 146% for the 130-139 weight index and 187% for the 140 plus weight index. The corresponding mortality ratio among women were 117, 129, 146 and 189% respectively. Data for age groups are presented on the next page.

MORTALITY RATIOS FROM ALL CAUSES OF DEATH BY AGE AND SEX IN RELATION TO DEATH RATES OF THOSE 90-109% OF AVERAGE WEIGHT

		Weight Index						
Age Group	Sex	080	080-089	090-109	110-119	120-129	130-139	140+
30-39	M	1.32	1.36	1.00	1.37	1.77	1.20	1.71*
	F	1.24	0.95	1.00	1.35	1.49	1.27	1.61
40-49	M	1.09	1.01	1.00	1.24	1.63	1.81	2.19
	F	1.20	0.94	1.00	1.09	1.38	1.51	2.02
50-59	M	1.24	1.02	1.00	1.18	1.34	1.51	2.02
	F	1.19	0.92	1.00	1.29	1.46	1.62	2.31
60-69	M	1.24	1.06	1.00	1.12	1.23	1.38	1.85
	F	1.19	0.96	1.00	1.27	1.37	1.59	1.85
70-79	M	1.32	1.12	1.00	1.06	1.08	1.30	1.41
	F	1.20	0.97	1.00	1.08	1.15	1.34	1.65
80-89	M	1.40	1.05	1.00	1.11	1.04	0.83	1.53
	F	1.21	1.07	1.00	0.95	0.99	1.04	1.10

*Mortality ratio based on only 5-9 observed deaths.

For all causes of death combined, the excess mortality among overweights was highest in the forties and fifties for both sexes and tended to diminish with advance in age. The excess mortality of underweights (below 80 weight index category) was generally somewhat higher among men than among women; the excess mortality among female underweights was uniformly about 20%.

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Ms. Oakar. Thank you very much, Doctor.

Dr. Silverman. Thank you, Dr. Sebok. My next colleague is Frank Funderburk from the Johns Hopkins University, who will present the highlights of his study.

Ms. Oakar. Well, this is an interesting study because you probably have heard your colleagues talk about it.

Dr. Funderburk. Yes.

Ms. Oakar. Too bad you couldn't have gone first.

STATEMENT OF DR. FRANK FUNDERBURK

Dr. Funderburk. In the minute that I've been allotted I don't think that I can adequately respond to the questions that have been raised.

Ms. Oakar. Please feel free to respond.

Dr. Silverman. Thank you.

Dr. Funderburk. I would be happy to submit to the committee additional information on this study and ask that that be entered into the record along with the written testimony that I've submitted today.

Ms. Oakar. In fairness to you, if you do want to respond to the specific points that they made, please feel free to do so. It's fine.

Dr. Funderburk. Thank you.

My name is Frank Funderburk and my scientific training is in experimental design and statistics. I'm part of a research team at the Johns Hopkins Medical School, which is under the direction of Dr. Ira Liebson.

Our group has conducted a series of studies on the effect of phenylpropanolamine in doses of 75 milligrams. This is the dosage that is currently marked in over-the-counter diet aids.

Phenylpropanolamine is also used widely in cough/cold preparations which are widely used.

Our studies at Hopkins were carefully controlled investigations in which more than 200 subjects were intensively studied over a 12-hour period. In our studies we found no overall clinically significant change in blood pressure or pulse as a result of phenylpropanolamine.

The subjects in the studies did not experience emotional highs or lows, as measured by standardized mood assessment and inventory techniques, and these emotional highs and lows are the effects that you would normally expect to find in drugs of abuse.

In response to the presentations that have been made earlier by Dr. Young and Dr. Mueller, we have done some analysis of the data on individual cases. And additional study is still going on with that. But we found increases in blood pressure in both placebo groups and subjects treated with phenylpropanolamine of large magnitude. We currently attribute those to a circadian variation and not to the effect of phenylpropanolamine. And as I say, I will be submitting additional information to the committee detailing those results.

[The following statement was subsequently received from Dr. Funderburk:]

SUPPLEMENTAL TESTIMONY SUBMITTED BY FRANK R. FUNDERBURK

In her recent Congressional Testimony, Bambi Batts Young of the Center of Science and Public Interest criticized the analyses and interpretation of studies of phenylpropanolamine (PPA) conducted at Behavioral Pharmacology Unit of The Johns Hopkins University School of Medicine. Since her statements are a matter of public record, we feel that it is important to point out the deficiencies in her analysis. Therefore, in this supplemental testimony, we will provide further details on the data from our studies, focusing on the points raised by Young's testimony.

OVERVIEW OF THE RESEARCH

The studies under discussion compared the effects of 75mg doses of PPA (in two dose forms) with those of matching placebo in carefully controlled clinical investigations (for details, see (1)). In one study ("parallel groups design"), 150 participants received either a 75mg sustained release PPA product, a 25mg immediate release PPA product at four hour intervals (for a daily total of 75mg) or a placebo (inactive product of "dummy pill"). Participants were studied for a 12 hour period following initial drug administration. The protocol called for measures of blood pressure (in three body positions), pulse, and subjective state throughout the session.

In the second study ("cross-over design"), 59 participants were tested, using a similar testing protocol, under both placebo and active drug conditions (75mg sustained release PPA). Data from both studies were analyzed using a statistical procedure (analysis of variance) which measured the effects of drug treatment (i.e., active drug versus placebo), time of measurement (i.e., time post-medication), and the interaction of these factors (i.e., did the drug treatments show statistically different effects over the course of the session). Further details on the statistical analysis is presented in our written testimony of July 21, 1983.

SUMMARY OF RESULTS

In the first study (of 150 cases), we found no statistically significant blood pressure differences between the groups receiving PPA and the one which received placebo. Normal fluctuations of blood pressure over the course of the day were found in both the active medications and placebo groups. No evidence of adverse subjective effects attributable to active drug treatment was noted.

In the second (cross-over) study, a statistically reliable difference between placebo and active PPA treatment was reported on several of the blood pressure variables indicating that the average blood pressure difference between the PPA and placebo was generally greater than zero. The actual differences ranged from .83mm Hg (standing systolic) to 3.37mm Hg (supine diastolic) with an average difference of less than 2mm Hg. Such small differences, although statistically reliable, were not regarded as clinically significant. No evidence of adverse subjective effects attributable to active drug treatment was noted.

SUMMARY OF YOUNG'S CRITIQUE

In her testimony, Bambi Batts Young argued that data from these studies were misinterpreted by the investigators. She claimed that here analysis indicated that the results of the Hopkins Study were consistent with those of Horowitz (1980) and indicated "alarming blood pressure increases" associated with PPA. Her argument centered on three major issues. She maintained that:

(1) Differences in time course of drug effects were ignored in the analysis (e.g., "unaccountably, after taking that whole sequence of measurements, the team lumped all readings from the PPA day into one average, and all the readings from the dummy-pill in another average, and noted that there was little difference between the two.").

(2) The group design and associated analysis precludes and/or obscures an analysis of individual responses to PPA (e.g., "if the average goes up . . . you can bet that the values for some individuals go a whole lot higher").

(3) Individual case reports provide some evidence of adverse PPA effects on blood pressure (e.g., "And if you look at the individual figures, that is exactly what you find.").

An objective evaluation of the analysis presented in support of her argument, however, indicates a misunderstanding of the basic scientific and statistical principles which were involved in our clinical evaluation of PPA effects. In the following section, we will briefly consider the basic scientific logic underlying clinical investigation of drug effects. Next we will discuss the results of the Hopkins Study considering each of Young's major points in some detail. Finally, we will summarize our conclusions in light of our original investigations, Young's arguments, our review of the evidence, and other relevant clinical data.

A BRIEF OVERVIEW OF CLINICAL RESEARCH

The purpose of conducting clinical drug evaluations is to better understand the nature of the effects of a drug. Although no single study—no matter how well controlled—can provide conclusive evidence of the presence or absence of a particular drug effect, clinical evaluations are designed to provide the best possible evidence possible in a particular research context. Well-controlled clinical trials follow a well-defined set of rules for describing and explaining the events which they are designed to study. These rules include empirical verification ("what did you see"), operational definition ("what were the criteria"), controlled observation ("when/how did you see this"), statistical verification ("how likely is this result") and empirical confirmation ("who else has found similar results"). The scientific value of any clinical evaluation depends on the extent to which the analysis follows these basic scientific rules. The well-controlled clinical trial will specify:

(1) The types of measures to be taken (empirical verification).

(2) The criteria for measuring responses of interest (operational definition).

(3) The circumstances under which measures will be taken, control for extraneous variables by various techniques, including random assignment to treatment (controlled observation).

(4) The type of statistical analysis to be used (statistical verification).

(5) The relationship of results/analysis to existing research (empirical confirmation).

Such rules allow researchers to make valid observations which eliminate or control (to the extent possible) extraneous variables which could influence the outcome of an experiment. In addition, adherence to these rules insures that the results of a particular study can be interpreted statistically (e.g., in terms of probability statements regarding a particular outcome). In this regard, it is important to note that in order to determine if a relationship exists, the information in both experimental and control conditions must be taken into account. (It is a very common mistake to draw conclusions based on relationships which appear in one condition without considering the other). Even then, however, the interpretation of the result of a particular study must be made with consideration to other relevant research findings. Let us now turn our attention to the "Hopkins Study".

A RESPONSE TO YOUNG'S CRITIQUE OF THE "HOPKINS STUDY"

The "Hopkins Study" was designed and conducted according to sound scientific methods. Data were analyzed using well established scientific and statistical procedures. The conclusions drawn from the studies were quite consistent with a large body of independent clinical research on PPA.

The overall conclusion from this investigative effort was that PPA in acute daily doses of 75mg did not have clinically significant adverse effects on blood pressure, pulse or mood.

Young maintained that our analyses overlooked a number of important factors, including time course of drug effects, limitations of group designs, and consideration of individual differences. As a result, she argues the conclusions drawn from this research are inappropriate. Let us consider each of her major points:

1. Were time course effects considered? Yes.

Young implied that the effects of the various drug treatments over time were obscured by presenting only "average" scores on the variables studied. This is simply not the case. The analysis of variance model used to analyze the data asked the following questions of the data:

(1) Were there any overall differences between drug treatments? (Main effect for drug treatment).

(2) Were there any trends/changes over the course of the session? (Main effect for measurement occasion).

(3) Did the various drug treatments have different effects at different times during the session (drug x measurement occasion interaction)?

As in most types of statistical analysis, these questions are answered in terms of the probability of finding differences between the various measures which are greater than those which would be expected by chance. Thus, even though one group may have a different average than another, either overall or at one point in time, the relevant question is whether this difference is greater than one would expect based on a random sampling from the population studied.

In our first study (n=150; parallel groups design), our analysis did not indicate any statistically reliable differences in blood pressure between the various drug treatments either overall or at the various measurement occassions, although (as expected) general fluctuations in blood pressure were observed over the course of the session for participants in all treatment groups. In our second study (n=59; cross-over design), we found a small, but statistically reliable, difference between drug treatments (averaging approximately 2 mm Hg) on most measures of blood pressure. In general, apart from random variation, these differences were constant over the course of the session. Subjects in both active drug and placebo conditions showed normal fluctuations over the course of the session.

2. Did the group design obscure important findings? No.

Young argues that group designs such as ours, obscure atypical responses ("outliers", in statistical jargon) in a treatment group. While such an occurrence is possible, a well-conducted analysis examines for such potential problems. Before conducting our formal statistical analyses, we examined our data in terms of both change from baseline (pre-session) and absolute peak effect. Some subjects did, indeed, show quite striking increases in blood pressure at some point in the session. However, as noted in our oral testimony on 21 July 83, such fluctuations occurred in *both* placebo and active drug treatment groups. Since these effects appeared to be random occurrences, independent of drug treatment condition, it was considered appropriate to include such scores in our overall analysis for all treatment groups. For example, in the parallel groups design, a subject in the placebo condition showed a supine blood pressure of 176/116 on one measurement occasion, while a similar reading (164/116) was observed in one subject in the 75mg sustained release group, and also in one 25mg t.i.d. group (154/110). Peak blood pressure readings of greater than 94mm Hg were found with approximately equal frequency in all three drug treatment groups in the parallel groups design, and this is shown in Table 1. Similar results were found in the cross-over design, as shown in Table 2.

3. Do individual case reports provide evidence of adverse PPA effects? No.

As noted above, many subjects treated with placebo showed dramatic blood pressure increases during the course of the session. In her testimony, Young showed cases in which blood pressure increased dramatically on the day they received active medication. Similar "dramatic" increases are also seen under placebo treatment. Figure 1 and 2 illustrate the problems associated with interpreting an individual's fluctuations in blood pressure over a long experimental session. Using Young's criterion, one would suspect that the "passing attack of serious hypertension" in these two subjects was the result of placebo (no drug). As noted above, the frequency of peak blood pressure readings over 94mm Hg was evenly distributed among the various treatment groups. An analysis of peak response (using analysis of variance procedures) applied to difference scores between baseline blood pressure and peak blood pressure also confirms this finding (see Table 3). In the parallel groups design, no statistically significant differences between peak blood pressure readings were found in any of the three body positions. In the cross-over design, only the supine diastolic difference measure was statistically reliable (mean difference=5.8mm Hg at peak). These findings are entirely consistent with the results presented in our reports to FDA and in our written testimony submitted on 21 July 83.

SUMMARY

The data reviewed in this supplemental testimony support our original conclusions regarding the effects of PPA in daily doses of 75mg. Our analyses suggest that this dose does not produce clincially significant increases in blood pressure even when peak blood pressure effects were examined. In our parallel groups design, slightly more "hypertensive" supine diastolic blood pressure readings were observed in the subjects treated with placebo (10 percent) as compared with PPA (6 percent). In the cross-over design, this pattern was reversed, with slightly more "hypertensive" supine diastolic readings in subjects treated with PPA (11.8 percent) as compared with placebo (5 percent). Neither of these differences is statistically reliable. Even smaller differences between active drug and placebo were found in peak measures taken while subjects were sitting or standing.

Young's analysis of the results of our study failed to consider a number of important factors. In particular, Young did not consider the results of our parallel groups study in which placebo treatment was more frequently associated with "hypertensive episodes". Nor did her analysis give adequate consideration to the possibility that many of the "hypertensive episodes" in both placebo and drug treatment groups could be attributed to normal circadian variation in blood pressure.

Her use of individual cases to illustrate "adverse" effects of PPA is particularly inappropriate since both routine statistical analyses and analyses of peak effects indicated very little systematic difference in blood pressure response between treatment groups in either the parallel groups design or in the cross-over design. The statistically reliable finding of small PPA-associated effects on supine diastolic blood pressure is consistent with our previous report. In the present study, the mean peak difference between treatments was 5.8mm Hg, while the average difference between treatments (over the session) was 3.37mm Hg, for supine diastolic blood pressure.

Our results are consistent with an extensive body of clinical literature suggesting that PPA, in the dose examined in our study, does not have adverse clinical effects on blood pressure, pulse, or mood.

TABLE 1.—PARALLEL GROUPS DESIGN—FREQUENCY OF PEAK OF DIASTOLIC BLOOD PRESSURES >94

Condition	Standing		Sitting		Supine	
	Yes	No	Yes	No	Yes	No
PPA 75(S.R.)	1	49	3	47	3	47
PPA 25 t.i.d.		50	1	49	4	46
Placebo		50	3	47	5	45

TABLE 2.—CROSS-OVER DESIGN—FREQUENCY OF PEAK DIASTOLIC BLOOD PRESSURE >94

Condition	Standing		Sitting		Supine	
	Yes	No	Yes	No	Yes	No
PPA 75(S.R.)	2	57	4	55	7	53
Placebo		59		59	3	56

TABLE 3(A).—PEAK INCREASE (FROM BASELINE) IN DIASTOLIC BLOOD PRESSURE—PARALLEL GROUPS DESIGN

Condition	Standing	Sitting	Supine
PPA 75 (S.R.)	5.40	9.32	14.08
PPA 25 t.i.d.	8.58	7.32	11.12
Placebo	8.12	6.46	11.00

TABLE 3(B).—PEAK INCREASE (FROM BASELINE) IN DIASTOLIC BLOOD PRESSURE—CROSS-OVER DESIGN

Condition	Standing	Sitting	[1] Supine
PPA 75 (S.R.)	11.39	7.27	15.39
Placebo	7.98	8.40	9.59

[1] $p < .01$.

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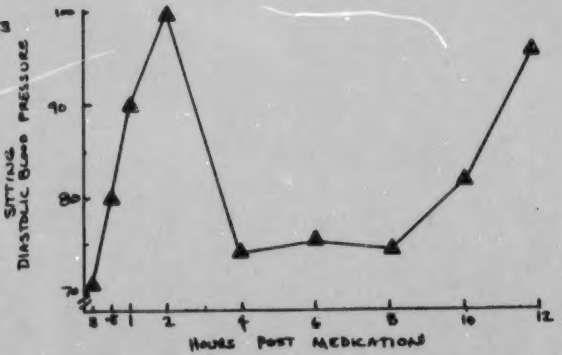
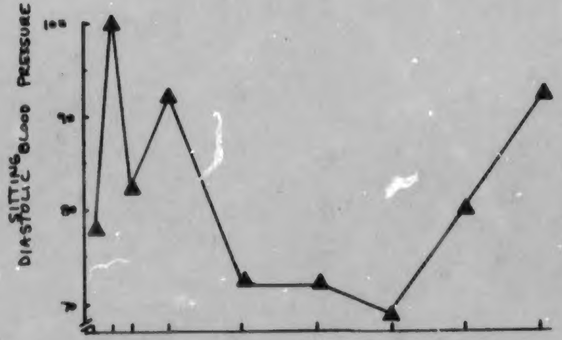


CASE # 63
PLACEBO

FIGURE
1



CASE # 69
PLACEBO

FIGURE
2

Dr. **Funderburk**. Thank you.

[The prepared statement of Dr. Funderburk follows:]

PREPARED STATEMENT OF FRANK FUNDERBURK, M.S., THE BEHAVIORAL PHARMCEUTICAL RESEARCH UNIT OF THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

Good morning. My name is Frank Funderburk. I have a Master's degree in biostatistics and am a collaborating investigator associated with the Behavioral Pharmacology Research Unit of the Johns Hopkins University School of Medicine in Baltimore, Maryland. I was part of the team, led by Dr. Ira Liebson, which conducted a number of studies of PPA. I would like to summarize the results of our research to you.

The focus of the research we have been doing on phenylpropanolamine has been studying its effects on mood alterations first. I am well aware that many of the critics of phenylpropanolamine state that the drug acts like amphetamine—or "speed"; that it produces a euphoric "high" in users.

In our studies we measured mood alterations using both subjective methods, where the subject is asked by the researcher how he feels; and, using objective methods, notably two scientifically accepted test scales that were designed specifically to measure alterations in mood states: the Addiction Research Center Inventory, and the Profile of Mood States.

In neither of these analyses did PPA show amphetamine-like effects. PPA was not related to either euphoria or sedation. In fact, in one of the only statistically findings in three studies of PPA, there was some evidence to suggest that if PPA produced any alterations in mood at all, it was to reduce the fatigue and boredom associated with a 12-hour experimental session in a relatively unstimulating laboratory environment.

This is not to say that no mood changes were observed over the course of a 12-hour experimental period. For example, most subjects had more energy in the morning than they did at the end of the day. They were all pretty bored by the end of the day—as one might expect. But, with the one exception I mentioned, these changes in how the subjects felt were identical in both tests and control groups.

Now, as for the effect of phenylpropanolamine on blood pressure: In one study we carried out on 150 subjects, we found no change in blood pressure that could be attributed to taking a 75 mg dose of PPA. Yes, there were changes over the 12-hour course of the study; and yes, there were differences in when these changes occurred between the test and control groups. But none of these differences reached statistical significance; all of them were within the range of what a medical observer would expect to see over the course of a day in a normal, healthy individual.

In another study of 59 individuals, we did observe some small differences in blood pressure between the subjects taking a 75 mg dose of PPA as compared to those taking a placebo. As a research scientist, I view these differences as statistically significant, and have reported them as such. But as a physician, Dr. Liebson did not regard these differences as clinically significant. The average overall difference in blood pressure between the two groups was less than 2 mm of mercury—that means blood pressure of, say 120 over 80 as compared to 122 over 82.

Our test methods involved giving 75 mg of phenylpropanamine to subjects either as one time-released dosages, or as three separate dosages of 25 mg each at four-hour intervals. In one test using 150 subjects, reactions were compared to a control group receiving a placebo on the same dosage schedule. In another test of 59 subjects, the participants served as their own controls; they took PPA on the test day, and, a week later, took a placebo, on the same dosing schedule. Both tests were carried out over a 12-hour period. Blood pressure, pulse and mood-alteration measurements were taken nine times: before any drugs were given, one half-hour after drugs were given, and then at hourly intervals.

Does PPA produce a "high"? No. Does taking it result in an amphetamine-like euphoria? No. Is it "speed"? No. In our scientifically controlled studies of 75 mg PPA we found none of the euphoric, sedative, or amphetamine-like effect normally associated with drugs of abuse. Further, we found no clinically significant changes in blood pressure, pulse or mood.

I am submitting my comments, and copies of the studies I referred to, to be entered into the record.

Thank you.

EFFECTS OF PHENYLPROPANOLAMINE ON BLOOD PRESSURE,
PULSE, AND MOOD:
PARALLEL GROUPS DESIGN

Study Site:
Behavioral Pharmacology Research Unit
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Date: October 8, 1982

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FINAL REPORT OF

CLINICAL PROTOCOL NO. 82-8(A)

An Evaluation of the Acute Effects of Phenylpropanolamine in Normal Volunteers: Parallel Groups Design

Sponsor: Thompson Medical Company, Inc.
919 Third Avenue
New York, NY 10022

Investigators: Ira Liebson
George Bigelow
Roland Griffiths
Frank Funderburk

Protocol developed by: The Clinical Consulting Group
ANTECH, Inc. and the
Behavioral Pharmacology Research Unit

Contact: Frank Funderburk
(301) 997-0880

Project start date: 25 June 82

Project completion date: 31 August 82

ABSTRACT

One hundred fifty (150) healthy normotensive volunteers (mean age = 25.9) participated in a double-blind, placebo controlled comparison of the effects of phenylpropanolamine HCL on blood pressure, pulse, and mood. Two dosage forms of phenylpropanolamine were studied (75 mg sustained release and 25 mg t.i.d.) in comparison with placebo. Subjects were randomly assigned to one of the three drug treatment conditions. Subjects in one group (Group A) received the 75 mg sustained release dose on their first medication occasion and placebo capsules on the other two dosing occasions. Subjects in another group received 25 mg capsules at each medication occasion (Group B). Subjects in the other group (Group C) received placebo at each medication occasion. Subjects were studied for a 12 hour testing session.

Measurements of blood pressure (sitting, standing, and supine), pulse, and subjective drug effect ("mood") were obtained 9 times during the session at baseline (prior to drug administration) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr post initial dosing.

Mixed design analysis of variance revealed no main effects for drug treatment on any of the measures. As expected, all measures showed main effects for time of day (circadian effects), indicating that subjects' physiological and subjective state changed over the course of the session. These changes were not, however, related to the drug treatment condition.

RATIONALE

PPA has been used as an anorexiant for over 40 years and has long been an ingredient in many over-the-counter cough-cold products (see, e.g., Silverman, 1980). Recently, however, some reports have appeared suggesting that PPA--generally in doses higher than those approved for over-the-counter use in the United States--may be associated with adverse hypertensive effects or other amphetamine-like side effects (e.g., Horowitz, 1980; Dietz, 1981).

Silverman et al. (1980) reported no adverse hypertensive effects of a 25 mg dose of PPA either alone or in combination with 100 mg of caffeine. Hoebel (paper in preparation, 1982) noted no adverse hypertensive effects of 150 mg PPA (75 mg b.i.d.) in a group of six normotensive individuals.

The present study was undertaken to extend the examination of PPA effects on blood pressure, pulse, and subjective state in a large, carefully controlled clinical investigation.

INVESTIGATIVE METHODS

Subjects

Subjects were 150 healthy normal volunteers (mean age = 25.9) (both male and female). The study population consisted of 83 caucasians, 63 blacks, 3 orientals, and 1 American Indian. Approximately 58% of the subjects were men. All had given informed consent and had been screened to meet the following criteria:

a. between 18 and 55 years of age

b. no current use of medications which would compromise the validity of the evaluation of the test products

c. no physical contraindications to consumption of PPA at the dose levels used in this study

d. no history of severe emotional disturbance, chronic alcoholism, or drug abuse

e. evidence that the subject would participate in the research and be cooperative

f. good general health based on a medical history interview conducted within one month of the study start and a recent physical examination

g. female subjects certified that they were not pregnant or nursing a baby for the duration of the study.

Design and Procedure

Subjects were randomly assigned to one of three treatment groups upon entry into the study. The basic investigative procedures followed for each subject are detailed below.

1. General Procedures

a. Subject control. Subjects were instructed to be free of all medications for the week prior to the first administration of a test product. Subjects who had ingested substances which could have compromised the validity of the study were excluded. Study medications were administered under clinical supervision. Subjects remained at the test facility for the entire testing period (approximately 13 hours) on the test day.

b. Meals and food restrictions. On test days subjects were provided with a choice of standard noontime meals. Foods containing xanthines (e.g., coffee, tea, cola) were not permitted on study days.

c. Drug administration. In this investigation two currently marketed doses of test products containing PPA (PPA, 25 mg, t.i.d. and 75 mg sustained release PPA) were being compared with placebo. On each test day subjects received three administrations of a test product. Study medications were identical in appearance and were labeled in code so that neither the investigator nor the subject could know which medication was being administered. Doses were given at 4 hour intervals (e.g., approximately 8:00 am, 12 noon, and 4:00 pm).

Subjects were randomly assigned to one of three treatment conditions. One group of subjects (Condition A) received the 75 mg sustained release product at their first dosing and matching placebo capsules on subsequent dosings. Another group of subjects (Condition B) received 25 mg PPA at each of the three dosings. Finally, one group (Condition C) received placebo at all three dosings. This dosing schedule is illustrated in Table 1.

Table 1

Dosing Schedule on a Test Day

	Dose 1 (approx. 8:00 am)	Dose 2 (approx. 12 noon)	Dose 3 (approx. 4:00 pm)
Condition A	75 mg sustained	placebo	placebo
Condition B	25 mg PPA	25 mg PPA	25 mg PPA
Condition C	placebo	placebo	placebo

d. Clinical measurements. Measures of blood pressure and pulse were obtained 9 times during each experimental session: Once prior to initial drug administration (0 hr) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr following initial drug administration. Blood pressure (sitting, standing, supine) was measured using procedures recommended by the American Heart Association (Kirkendall et al., 1980). Clinical measures of subjective state were obtained using visual analogue mood-scales on which subjects indicated the extent to which they felt a drug effect and their subjective impression of that drug effect. These measures were supplemented by subjective reports of subjects and the observations of research staff.

2. Design

This study may be viewed as a 3 (drug treatment conditions) x 9 (measurement occasions) mixed design. Mixed design analysis of variance procedures were used to evaluate data from this component of the study. Separate analyses were conducted for each of the dependent variables. Factors in the analysis were drug treatment assignment (Condition A vs B vs C) and measurement occasion (0 hr, 1/2 hr, etc.). Treatment assignment was a between-groups factor while measurement occasion was a within-subjects factor. For all tests involving repeated measures factors, a conservative F test was used in evaluating statistical significance (see, e.g., Geisser & Greenhouse, 1958).

RESULTS

Specific results of the analysis of variance for each of the variables studied are summarized below.

Pulse tended to increase slightly over the course of the session (F = 16.67, $p < .01$) for subjects in all treatment conditions. No main effect for drug treatment was identified.

Standing systolic blood pressure was generally higher later in the session (F = 4.34, $p < .05$) for subjects in all treatment groups. This trend was more marked for subjects in the placebo group (F = 3.39, $p < .05$). No main effect for drug treatment condition was identified. Standing diastolic blood pressure was generally lowest at 8-10 hours post initial medication for subjects in all treatment groups (F = 13.80, $p < .01$). No main effects for drug treatment was identified.

Sitting systolic blood pressure was generally lowest at 1-4 hours post medication (F = 4.01, $p < .05$). Subjects in the 75 mg sustained release treatment group tended to show decreased sitting systolic blood pressure later in the session as compared with subjects in the 25 mg t.i.d. or placebo groups (F = 3.65, $p < .05$). Sitting diastolic blood pressure was generally lower at 4-8 hours post dosing for subjects in all treatment groups (F = 11.22, $p < .01$). No main effect for drug treatment was identified. These results are shown in Figure 1 (attached).

Supine systolic blood pressure was generally higher later in the session (F = 11.09, $p < .01$). This increase tended to be largest in the placebo treatment group (F = 4.44, $p < .05$). No main effect for drug condition was identified. Supine diastolic blood pressure tended to be lowest at 6-10 hours post initial dosing (F = 17.70, $p < .01$). No main effect for drug condition was identified.

Subjective measures of drug effect and mood revealed no significant differences between the three drug conditions. There were, however, significant changes in mood over the course of the session. These included measures of "drug effect" ($F = 8.53$, $p < .01$), ratings of feeling "good" ($F = 6.35$, $p < .01$), ratings of feeling "bad" ($F = 5.30$, $p < .01$), and ratings of drug liking (F 5.30, $p < .01$) over the course of the session. In general, subjects in all treatment groups (including placebo) reported feeling better (more pleasurable) early in the session and more dysphoric later in the session. These variations in subjective state, although statistically reliable, were very small and were not considered clinically relevant. Figure 2 illustrates these effects.

Summary tables of means, standard deviations and analysis of variance results for each variable studied are presented in the Appendix to this report.

DISCUSSION

The present study evaluated the acute effects of two dosage forms of phenylpropanolamine (75 mg sustained release, 25 mg t.i.d.) in comparison with placebo. Measures of drug effect on pulse, blood pressure (sitting, standing, and supine) and subjective state ("mood") were obtained over a 12-hour testing period.

No significant main effects for drug treatment were observed on any of the measures. Differences in blood pressure between drug treatment groups was very small. No consistent pattern of differences between drug treatments was observed. On some measurement occasions, subjects receiving active drug treatments showed higher mean blood pressures than did subjects receiving placebo treatment. On other occasions, this effect was reversed. No statistically significant differences between drug treatments were found on any of the measurement occasions.

As expected, statistically significant differences in blood pressure were found over the course of the daily session. Circadian variation of blood pressure is well documented (see, e.g., Millar-Craig, Bishop, & Raftey, 1978). Our results are consistent with this literature.

The present results also suggest that PPA, in the dosage forms studied, had no systematic effect on subjective ratings of drug effect or drug liking. No statistically reliable differences between drug treatments were observed on measures of drug effect or drug liking. The effects of the two PPA treatments were not rated as any better or any worse than that of the placebo. This finding is consistent with that of Seppala, Nuotto, and Korttila (1981) in that no significant euphoric effects were noted for subjects treated with PPA. As was the case with blood pressure, subjective state ("mood") showed circadian changes over the course of the session. In general, subjects in all treatment groups reported feeling "better" early in the session as compared with later in the session.

Overall, the present findings suggest that phenylpropanolamine (in the dosage forms studied) is not associated with adverse effects on blood pressure, pulse, or mood.

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AN EVALUATION OF THE ACUTE EFFECTS OF PHENYLPROPANOLAMINE IN NORMAL VOLUNTEERS: (CROSSOVER DESIGN)

Study Site:	Behavioral Pharmacology Research Unit Johns Hopkins University School of Medicine Baltimore City Hospitals D-5-West 4940 Eastern Avenue Baltimore, Maryland 21224
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Date:	October 22, 1982

FINAL REPORT OF
CLINICAL PROTOCOL NO. 82-8(A)

An Evaluation of the Acute Effects of Phenylpropanolamine in Normal Volunteers: (Crossover Design)

Sponsor:
Thompson Medical Company, Inc.
919 Third Avenue
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Protocol developed by:
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Behavioral Pharmacology Research Unit

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Project Start Date: 25 June 82

Project Completion Date: 31 August 82

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ABSTRACT

Fifty-nine (59) healthy normotensive volunteers (mean age = 25.5) participated in a double blind, placebo controlled crossover evaluation of the effects of a 75 mg sustained release dosage form of phenylpropanolamine HCl on blood pressure, pulse, and mood. Each subject participated in two experimental sessions, one under placebo and the other under the active drug treatment. Order of exposure to treatment conditions was randomly determined.

Measurements of blood pressure (sitting, standing, and supine), pulse, and subjective drug effect ("mood") were obtained 9 times during the session - at baseline (prior to drug administration) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr post-initial dosing.

Mixed design analysis of variance revealed no statistically significant main effects for drug treatment on measure of pulse or mood. Nearly all blood pressure measures (the standing systolic measure was an exception) showed statistically reliable - but clinically insignificant - differences between placebo and the active drug condition. In all cases, the mean blood pressure was slightly higher under the active drug treatment. The magnitude of this effect, however, was extremely small (the mean differences ranged between .83 and 3.37 mm Hg).

As anticipated, most measures showed main effects for time of day (circadian effects), indicating that the subjects' physiological and subjective state changed over the course of the session. These changes were, however, generally independent of the drug treatment condition. This study suggests that the 75 mg sustained release dosage form of phenylpropanolamine has minimal - and clinically insignificant - effects on the blood pressure, pulse, or mood of normotensive individuals.

An Evaluation of the Acute Effects of Phenylpropanolamine in Normal Volunteers: (Crossover Design)

INTRODUCTION

Phenylpropanolamine hydrochloride (PPA) is a synthetic compound with actions similar to ephedrine. However, PPA is generally believed to produce less CNS stimulation than ephedrine. PPA is currently marketed over-the-counter (OTC) in the United States in both as a nasal decongestant and as a weight control aid. Recently the FDA and others have raised questions about the safety and appropriateness of OTC availability of PPA (Federal Register, Vol. 47, No. 39, 1982; Horowitz, 1980; Dietz, 1981; Lancet, 1982). In their publication, the agency requested additional information on the effects of PPA on a variety of safety parameters including blood pressure, pulse, and self-reported side effects. In the present report, crossover experimental design was used to compare the effects of 75 mg sustained release PPA with placebo on these parameters. Fifty-nine normotensive adults were studied over a time course of 12 hours.

OBJECTIVE AND RATIONALE

This study was designed to extend previous research conducted in our laboratory (Funderburk et al., 1982). In that investigation, 150 normotensive adults participated in a study comparing the effects of two dosage forms of PPA (25 mg t.i.d., 75 mg sustained release) with placebo. No significant main effects for drug treatment were found on any of the measures of blood pressure, pulse, or mood. Although the relatively large sample size in that study provided considerable statistical power, it was believed that an even more sensitive comparison would be afforded by a crossover study in which each subject would serve as his own control.

Several studies have investigated the acute effects of PPA in normal subjects (e.g., Silverman et al., 1980; Hoebel, 1982). However, these studies have generally involved rather small subject samples and have, therefore, had relatively low statistical power. The recent study in our laboratory, however, (Funderburk et al., 1982) which employed 150 subjects in a parallel groups design provided a rather powerful test of the effects of PPA on normal subjects. The present study, using a crossover design, was implemented to provide an even more powerful evaluation of PPA effects in a large group of normal volunteers.

INVESTIGATIVE METHODS

Subjects

Subjects were 59 normal volunteers (both male and female, mean age = 25.5). The study population consisted of 33 caucasians, 25 blacks, and 1 American Indian. All had given informed consent and had been screened to meet the following criteria:

a. between 18-55 years of age
b. no current use of medications which would compromise the validity of the evaluation of the test products
c. no physical contraindications to consumption of PPA at the dose levels used in this study
d. no history of severe emotional disturbance, chronic alcoholism, or drug abuse

e. evidence that the subject would participate in the research and be cooperative

f. good general health based on a medical history interview conducted within one month of the study start and a recent physical examination

g. female subjects certified that they were not pregnant or nursing a baby for the duration of the protocol.

Design and Procedure

Subjects were randomly assigned to one of two treatment sequences. One group (n = 30) received the placebo treatment on their first testing occasion and the 75 mg sustained release treatment on the second testing session. This order of treatment was reversed for subjects in the other group (n = 29). The two treatment sessions were always separated by at least one washout day to minimize any possible treatment carryover effects. The basic investigative procedures followed for each subject are detailed below.

1. General Procedures

a. Subject control. Subjects were instructed to be free of all medications for the week prior to the first administration of a test product. Subjects who had ingested substances which compromised the validity of the study were excluded. Study medications were administered under clinical supervision. Subjects remained at the test facility for the entire testing period during test days.

b. Meals and food restrictions. On test days subjects were provided with a choice of standard noontime meals. Foods containing xanthines (e.g., coffee, tea, cola) were not permitted on study days.

c. Drug administration. In this investigation a currently marketed dose of a test product containing PPA (75 mg sustained release PPA) was compared with placebo. On each test day subjects received three administrations of a test product (either active medication or placebo). Doses were given at 4 hour intervals (e.g., approximately 8:00 am, 12:00 noon, and 4:00 pm).

Subjects were randomly assigned to one of two treatment conditions on the first test day. One group of subjects (Group A) received the 75 mg sustained release product at their first dosing and matching placebo capsules on subsequent dosings. The other group (Group B) received placebo at all three dosings. After at least one washout day, the subjects returned to complete the second leg of the crossover. During this session, they received the treatment not administered on the first day. This dosing schedule is illustrated in Table 1.

Table 1

Dosing Schedule

		Dose 1 (approx. 8:00 am)	Dose 2 (approx. 12 noon)	Dose 3 (approx. 4:00 pm)
Session One	Group A	75 mg sustained	placebo	placebo
	Group B	placebo	placebo	placebo
Session Two	Group A	placebo	placebo	placebo
	Group B	75 mg sustained	placebo	placebo

d. Clinical measurements. Measures of blood pressure and pulse were obtained 9 times during each experimental session: Once prior to initial drug administration (0 hr) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr following initial drug administration. Blood pressure (sitting, standing, supine) was measured using procedures recommended by the American Heart Association (Kirkendall et al., 1980). Clinical measures of subjective state were obtained using analogue ratings of drug effects. These measures were supplemented by subjective reports of subjects and the observations of research staff.

2. Design

This study may be viewed as a 2(drug treatment conditions) x 2(orders of treatment administration) x 9(measurement occasions) mixed design. Mixed design analysis of variance procedures were used to evaluate data from this component of the investigation. Separate analyses were conducted for each of the dependent variables. Factors in the analysis were drug treatment condition (75 mg sustained release vs. placebo), order of treatment administration (active drug first vs. placebo treatment first), and measurement occasion (0 hr, 1/2 hr, etc.). Order of treatment administration was a between groups factor while drug treatment and measurement occasion were within subject factors. For all tests involving repeated measures factors, a conservative F test was used in evaluating statistical significance (see, e.g., Geisser & Greenhouse, 1958).

RESULTS

Specific results of the analysis of variance for each of the variables studied are summarized below.

Pulse tended to increase slightly over the session showing a peak at approximately 6 hours post-dosing ($F = 9.45$, $p < .01$). This effect occurred under both drug treatment conditions. No main effect for drug treatment was identified. No other main effects or interactions were identified.

Standing systolic blood pressure was relatively stable for subjects in both drug treatment groups. No main effects or interactions were identified.

Standing diastolic blood pressure tended to be slightly higher under the active drug treatment than under placebo. Although this effect was statistically reliable ($F = 7.41$, $p < .01$), the overall magnitude of the effect was small (mean difference between treatments = 2.26 mm Hg). Under both treatment conditions, standing diastolic blood pressure tended to show peaks at 4 and 12 hours post-initial dosing ($F = 6.81$, $p < .01$).

Sitting systolic blood pressure tended to be slightly higher under the active drug treatment than under placebo ($F = 4.46$, $p < .05$). The mean difference between treatments was 2.09 mm Hg. No other main effects or interactions were identified.

Sitting diastolic blood pressure tended to peak at 4 and 12 hours post-initial dosing under both treatment conditions ($F = 5.26$, $p < .05$). Overall, sitting diastolic blood pressure tended to be higher under the active drug treatment than under placebo ($F = 11.28$, $p < .01$). The mean difference between treatments was 2.75 mm Hg. No other main effects of interactions were identified.

Supine systolic blood pressure tended to peak at 4 and 12 hours post-initial dosing under both treatment conditions ($F = 7.33$, $p < .01$). The peak effect at 4 hours was most evident for subjects under the active drug treatment (resulting in a drug x time interaction, $F = 4.10$, $p < .05$). Overall, supine systolic blood pressure tended to be higher under the active drug treatment than under placebo ($F = 7.35$, $p < .01$). The mean difference between treatments was 2.52 mm Hg. No other main effects or interactions were identified.

Supine diastolic blood pressure tended to peak at 4 and 12 hours post-initial dosing under both treatment conditions ($F = 6.22$, $p < .05$). Overall, supine diastolic blood pressure tended to be higher under the active drug treatment than under placebo ($F = 11.91$, $p < .01$). The mean difference between treatments was 3.37 mm Hg. The time course of this drug effect was slightly different for the two treatment orders (4.15, $p < .05$). No other main effects or interactions were identified.

Subjective measures of drug effect and mood revealed no significant differences between the drug treatment conditions on any of the measures studied (rating of "drug effect," rating of "feeling good," rating of "feeling bad," and rating of "drug liking"). Ratings of "drug effect" tended to peak at approximately 6 hours post-initial dosing under both treatment groups. No other main effects or interactions were identified for any of the subjective measures.

Summary tables of means, standard deviations, and analysis of variance results for each variable studied are presented in the Appendix to this report.

DISCUSSION

The present study evaluated the acute effects of a 75 mg sustained release dosage form of phenylpropanolamine in comparison with placebo. A crossover design, in which each subject served as his own control, was used. Measures of drug effect on blood pressure (sitting, standing, and supine), pulse, and subjective state ("mood") were obtained over a 12-hour testing period.

As in our previously reported study (Funderburk et al., 1982), overall differences between phenylpropanolamine and placebo on measures of blood pressure were very small. In the present study, however, statistically reliable differences between the active drug and placebo were identified. This result can be attributed to the increased statistical power of the present design. As compared with our previous investigation, the present study had both a larger sample size per group (n = 59 vs. n = 50) as well as a lower overall error variance (a result of using each subject as his own control). Both of these features of the design served to increase statistical power. Under such conditions, it is quite possible to identify statistically reliable effects which are clinically trivial (see, e.g., Cohen, 1965). In the present study, for example, mean blood pressure differences between drug treatment conditons ranged from .83 mm Hg (standing systolic) to 3.37 mm Hg (supine diastolic) with an average overall difference of less than 2 mm Hg. Obviously, such small overall effects are not regarded as clinically significant.

As expected, statistically significant differences in blood pressure were generally found over the course of the daily session. This finding is consistent with the literature on circadian variation of blood pressure (see, e.g., Bock & Kreuzenbeck, 1966; Millar-Craig et al., 1978; Richardson et al., 1964; Rose, 1980). Drug treatment did not appear to affect these normal circadian variations. This result is consistent with our previous report.

The present study also replicated our previous investigation with respect to subjective drug effects. Overall our analysis failed to reveal any systematic differences between the drug treatments on subjective ratings of drug effect or drug liking. The effect of the active drug was not rated as any better or any worse than that of the placebo. Somewhat less circadian variability in subjective effect was observed in this study as compared with our previous investigation.

Overall, the results of the present study are quite compatible with the results presented in our previous report. Although statistically reliable effects on blood pressure were noted for the 75 mg sustained release dosage form of phenylpropanolamine, these effects were extremely small and were not considered clinically relevant. Likewise, no adverse effects were noted on pulse or subjective state.

More comprehensive work is needed in the area of PPA effects on mood and in the relationship between the physiological and psychological effects of the drug. Other areas for future investigation include an evaluation of PPA effects on specialized patient populations (e.g., hypertensives, obese) and over a wider range of doses.

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Supplement to Clinical Protocols

82-8(A) and 82-8(B)

EVALUATION OF PHENYLPROPANOLAMINE (75 mg) EFFECTS ON STANDARDIZED MEASURES OF DRUG EFFECT AND AFFECTIVE STATE

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Date: December 6, 1982

SUPPLEMENT TO CLINICAL PROTOCOLS
82-8(A) and 82-8(B)

Evaluation of Phenylpropanolamine Effects on Standardized Measures of Drug Effect and Affective State

Sponsor:
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ABSTRACT

Additional analysis was undertaken on data collected as part of Clinical Protocols 82-8(A) and 82-8(B). These analyses focused on a comparison of subjective PPA effects with those of other CNS-active drugs and a more rigorous evaluation of PPA effects on affective state ("mood"). These analyses indicated that PPA, in doses of 25 mg t.i.d. or 75 mg sustained release, were not associated with euphoria, amphetamine-like reactions, or sedation. Some evidence was found which suggested that PPA functioned to reduce the fatigue and boredom associated with a 12 hour experimental session in a relatively unstimulating environment.

INTRODUCTION

Previous reports from our laboratory (Funderburk et al., 1982a, 1982b) examined the effects of phenylpropanolamine (PPA) on blood pressure, pulse, and mood (including subjective ratings of drug effect) in normal volunteers. In a large sample (N = 150) parallel groups design study, PPA doses of 25 mg t.i.d. and 75 mg sustained release were found to have minimal effects on clinical measurements of blood pressure, pulse, or subjective ratings of drug effect and drug liking over a 12-hour experimental session. The authors concluded that PPA at the dose levels studied was not associated with adverse effects on the clinical measures studied. This conclusion received further support in a statistically more powerful crossover study (N = 59) which compared the 75 mg sustained release formulation with placebo on these same measures.

The present report is a supplement to Protocols 82-8(A) and 82-8(B). It describes additional analysis undertaken to provide additional information on the subjective effects of PPA. Particular attention will be focused on two key issues of concern: (1) A comparison of PPA with other CNS-active drugs and (2) A more rigorous evaluation of PPA effects on affective state ("mood"). In both instances our measures will be derived from widely used and well standardized psychometric instruments which have been proven sensitive to the effects of CNS drugs.

INVESTIGATIVE METHODS

Subjects. Subject characteristics are identical to those described in our previous reports. In the parallel groups design 150 healthy normal

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subjects participated (N = 50 in each of three experimental groups). In the crossover study 59 healthy normal subjects participated (each being exposed to each of two experimental conditions).

Design and Procedure.

The measures described in this report were obtained from subjects who participated in Clinical Protocols 82-8(A) [parallel groups design] and 82-8(B) [crossover design]. Two standardized test forms were administered to subjects prior to each clinical measurement occasion. One form was a short version of the Addiction Research Center Inventory (ARCI). This test allows comparison of PPA subjective effects with those of other CNS-active drugs. The other form was the Profile of Mood States (POMS). This test allows an evaluation of changes in affective state associated with drug treatment. Each form generally required less than 5 minutes to administer. More detailed descriptions of these tests follows:

Addiction Research Center Inventory (ARCI). Detailed description of the ARCI scales was given by Haertzen (1974). The empirical drug scales on this inventory were developed by selecting items which differentiated placebo from a variety of drugs including morphine, pentobarbital, chlorpromazine, LSD, amphetamine, pyrahexyl, and alcohol. In addition, clusters of items were developed (group variability scales) which combined items from the various scales to reflect patterns of drug effects. The scales used in this study, and the characteristics which they reflect are:

(1) AMP: empirical scale which measures similarity to amphetamine effects.

(2) BG: group variability scale which measures similarity to benzedrine effects. Interpreted as a measure of intellectual efficiency and energy.

(3) MBG: group variability scale which measures a morphine-benzedrine effect. Interpreted as a measure of euphoria.

(4) PCAG: group variability scale which measures pentobarbital-chlorpromazine-alcohol effects. Interpreted as a measure of sedation, fatigue, and low motivation.

(5) LSD: empirical scale which measures similarity to LSD effects. Interpreted as a measure of anxiety, tension, difficulty in concentration, depersonalization, and psychomimetic changes. Also interpreted as a measure of dysphoria.

Profile of Mood States (POMS). The POMS scales provide a means of assessing transient, fluctuating mood states. These scales were developed by factor analytic methods in a variety of subject populations including both normals and specialized patient populations (see, McNair, Lorr, and Droppleman, 1971, for a more detailed discussion of the development of these scales). The POMS has been found to be a sensitive measure of the effects of various experimental manipulations (including drug administration) in normal volunteers. The POMS measures six identifiable mood or affective states as well as various specialized affective states and global mood. The scales used in this study were:

(1) Tension-Anxiety
(2) Depression-Dejection
(3) Anger-Hostility
(4) Vigor-Activity
(5) Fatigue-Inertia
(6) Confusion-Bewilderment
(7) "Friendliness"
(8) Total Mood Disturbance.

Statistical Analysis. Data were analyzed using mixed design analysis of variance. Separate analyses were conducted for each of the dependent variables. In the parallel groups design factors in the analysis were drug treatment assignment (placebo, 25 mg t.i.d., 75 mg sustained release) and measurement occasion (0 hr, ½ hr, etc.). Treatment assignment was a between-group factor while measurement occasion was a within-subjects factor. Factors in the crossover design were drug treatment assignment, order of treatment administration (placebo first *vs*. active drug first), and measurement occasion. Order of drug administration was a between groups factor while drug treatment and measurement occasion were within subject factors. In both analyses tests involving repeated measures were evaluated using a conservative *F* test (e.g., Geisser and Greenhouse, 1953).

Results: Parallel Groups Design

Specific results of the analysis of variance for each of the variables studied are summarized below:

ARCI Variables

AMP. No main effect for drug treatment condition was identified. A significant main effect for measurement occasion was found ($F = 3.91$, $p<0.05$) reflecting a general decrease in AMP scores over the session for subjects in all treatment groups. No significant interactions were identified.

BG. No main effect for drug treatment condition was identified. A significant main effect for measurement occasion was found ($F = 4.80$, $p<0.05$) reflecting a general decrease in BG scores over the session for subjects in all treatmenr groups. No significant interactions were identified.

MBG. No significant main effects or interactions were identified.

PCAG. No main effects or interactions were found for drug treatment. A significant main effect for measurement occasion was identified ($F = 7.46$, $p<0.01$) which reflected a tendency for sedation (PCAG score) to be lowest early and late in the session as compared with the middle of the session. This general trend was present in all drug treatment groups. No other main effects or interactions were identified.

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POMS Variables

Tension-Anxiety. No significant main effects or interactions were identified.

Depression-Dejection. No significant main effects or interactions were identified.

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*LSD. No significant main effects or interactions were identified.

Anger-Hostility. No significant main effects or interactions were identified.

Vigor-Activity. No main effects or interactions were found for drug treatment. A significant main effect for measurement occasion was identified ($F = 10.37$, $p<0.01$) reflecting a general decrease in vigor over the course of the session. This general trend was present in all drug treatment groups. No other main effects or interactions were identified.

Fatigue-Inertia. No significant main effects or interactions were identified.

Confusion-Bewilderment. No significant main effects or interactions were identified.

"Friendliness." No main effect for drug treatment condition was identified. A significant main effect for measurement occasion was found ($F = 19.98$, $p<0.01$) reflecting a general decrease in "friendliness" over the course of the session for subjects in all drug treatment groups. No significant interactions were identified.

Total Mood Disturbance. No significant main effects or interactions were identified.

Results: Crossover Design

Specific results of the analysis of variance for each of the variables studied are summarized below:

ARCI Variables

AMP. No significant main effects or interactions with drug treatment were identified. A significant main effect for time course was identified ($F = 3.14$, $p<0.05$) which reflected a general decrease in scores over the course of the session for subjects in both drug treatment groups.

BG. No significant main effects or interactions with drug treatment were identified. A significant main effect for time course was identified ($F = 3.56$, $p<0.05$) which reflected a general decrease in scores over the course of the session for subjects in both drug treatment groups.

MBG. No significant main effects or interactions with drug treatment were identified. A significant main effect for time course was identified ($F = 5.40$, $p<0.05$) which reflected a general decrease in scores over the session for subjects in both drug treatment groups.

PCAG. A significant main effect for drug treatment was identified ($F = 4.97$, $p<0.03$). Overall subjects reported lower PCAG scores (reflecting less fatigue) under the 75 mg PPA treatment as compared with placebo. This effect was strongest in subjects who received the 75 mg PPA dose in their second session ($F = 5.72$, $p<0.02$). A main effect for time course was also identified ($F = 2.57$, $p<0.05$) which reflected a general increase in PCAG scores over the course of the session for subjects in both drug treatment groups. No drug x time interaction was identified.

LSD. A significant main effect for drug treatment was identified ($F = 7.69$, $p<0.01$). Overall subjects reported lower LSD scores (reflecting less dysphoria) under the 75 mg PPA treatment as compared with placebo. No other main effects or interactions were identified.

POMS Variables

Tension-Anxiety. A main effect for drug treatment was identified ($F = 4.86$, $p<0.05$). Overall subjects obtained lower tension and anxiety scores under the 75 mg PPA treatment as compared with placebo treatment. No other main effects or interactions were identified.

Depression-Dejection. No significant main effects or interactions were identified.

Anger-Hostility. A main effect for drug treatment was identified ($F = 5.27$, $p<0.025$). Overall subjects obtained lower anger-hostility scores under the 75 mg PPA treatment as compared with placebo treatment. No other main effects or interactions were identified.

Vigor-Activity. No main effects or interactions for drug condition were identified. A main effect for measurement occasion ($F = 5.23$, $p<0.05$) was identified which reflected a general tendency for subjects to obtain lower vigor-activity scores over time. No other main effects or interactions were identified.

Fatigue-Inertia. No significant main effects for drug treatment, order, or time course were identified. A drug x order interaction ($F = 8.64$, $p<0.01$) was identified which reflected the fact that greater fatigue was reported under placebo as opposed to 75 mg PPA in one group of subjects while the opposite trend was present in the other group of subjects. No other significant interactions were identified.

Confusion-Bewilderment. A significant main effect for drug condition was identified ($F = 7.00$, $p<0.01$). Overall subjects obtained lower Confusion-Bewilderment scores under the 75 mg PPA treatment than under placebo. No other main effects of interactions were identified.

"Friendliness." No significant main effects or interactions with drug treatment were identified. A significant time course effect was found ($F = 6.62$, $p<0.01$) which reflected a general tendency for "friendliness" to decrease over the course of the session, although friendliness scores did tend to increase at the last measurement occasion.

Total Mood Disturbance. No significant main effects or interactions were identified.

DISCUSSION

The present study evaluated the acute subjective effects of two dosage forms of PPA (75 mg sustained release, 25 mg t.i.d.) in comparison with placebo in a parallel groups design. These assessments were repeated in a crossover design which compared the 75 mg sustained release dose with placebo. Measures obtained included a comparison of PPA effects with those of a variety of CNS-active drug effects as well as an evaluation of PPA effects on various affective states.

In the parallel groups design PPA effects were not different from those of placebo on any of the measures studied. Subjects in all groups tended to feel more sedated or tired as the session progressed, with lessening of the sedative effect prior to the conclusion of the session. The extent and nature of this effect was not related to drug treatment.

In the more powerful crossover design some statistically reliable differences between the 75 mg sustained release PPA treatment and placebo were identified. In particular, on the ARCI scales the 75 mg PPA treatment was associated with less sedation-fatigue and less dysphoria during the course of the session as compared with placebo. However, no evidence of amphetamine-like effects or euphoria was found. As expected, most measures showed reliable circadian effects over the course of the session. As in our previous studies, these effects indicated that subjects generally felt "better" early in the sessions as compared with later in the session. The POMS measures provided further confirmation of these effects. Subjects reported feeling less tense or anxious, less hostile, and less confused under the 75 mg PPA treatment as compared with placebo.

The pattern of results in the present study is consistent with that found in our previous analysis of PPA mood effects (Funderburk et al., 1982a 1982b) and with the findings of Seppala et al. (1981). Overall no reliable euphoric effects were noted for PPA, although there is some evidence that PPA functioned to reduce the dysphoria and boredom associated with a 12-hour experimental session in the restricted and relatively bland environmental setting of a research laboratory. Thus, it appears that PPA may serve to increase mental alertness and reduce fatigue in relatively unstimulating settings.

In the doses studied PPA did not produce a pattern of subjective effects which would be indicative of high abuse liability. The absence of euphoric or amphetamine-like effects or sedative-type effects suggest that PPA is not likely to be knowingly chosen as a drug for self-administration by someone seeking such psychological effects. Such an interpretation is consistent with our previous finding that ratings of "drug liking" for PPA were not different from those of placebo.

Overall the present findings suggest that PPA may have mildly beneficial effects on affective state in that it increases alertness and reduces dysphoria. The magnitude of these effects, however, is not large. Further these findings may be limited to affective states measured under unusually low levels of environmental stimulation. At the same time, no evidence of amphetamine-like or euphoric effects were noted even in the more powerful crossover design.

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Ms. **Oakar**. Thank you, Doctor.

Dr. **Silverman**. Thank you. Next we will hear from my colleague, Dr. Coons, professor of psychology at New York University. Dr. Coons?

STATEMENT OF EDGAR COONS

Dr. **Coons**. Good afternoon. My name is Edgar Coons. I hold a Ph. D. degree in psychology from Yale. I am a professor of psychology at New York University and a former chairman of its psychology department. My research specialty is physiological psychology.

I have with me written testimony on my research on phenylpropanolamine [PPA] which I would like to submit for the record.

Dr. **Coons**. I would also like to present to you the main points of that testimony. In my research I used rats who were implants with an electrode in the part of the brain that controls both the appetite and the feeling of reward. When electrically stimulated, these rats would begin to feed even when thoroughly satiated.

Pretreatment of these rats with PPA significantly increased the amount of electrical current required to make the rats eat, showing the effectiveness of PPA as an appetite suppressant.

Rats can also be trained to stimulate themselves with the current to produce a feeling of reward. PPA did not decrease the amount of current needed for reward, indicating that it had no rewarding or behavioral stimulant properties of its own.

This result was markedly different when d-amphetamine was used. That drug greatly decreased the amount of current needed for self-stimulation, indicating that contrary to PPA, d-amphetamine, while also an effective appetite suppressant, has considerable stimulant or euphoragenic properties.

Animal studies provide very useful, objective evidence of the effectiveness of appetite suppressants because, and this is important, animals are not affected by such factors as advertising, motivation, or the social pressures to be thin. My studies with rats lead me to conclude that PPA is an effective appetite suppressant that has no stimulant or euphoragenic properties.

Thank you.

[The prepared statement of Dr. Coons follows:]

Prepared Statement of Edgar E. Coons, Ph. D., Professor of Psychology, New York University

Good morning. My name is Edgar E. Coons. I hold a Ph. D. degree in psychology. I am a professor of psychology at New York University and the former chairman of its Psychology Department. My research specialty is physiological psychology.

I have been actively involved in the study of appetite control mechanisms since 1957, when I discovered that a region of the rat brain, the lateral hypothalamus, can produce feelings of hunger or fullness, as well as euphoria when electrically stimulated. Rats and other animals are very useful models for studying the effects of appetite suppressants because they provide objective evidence of changes in feeding behavior and weight loss since animals are not affected by such factors as advertising, motivation, or the social pressure to be thin.

The study I would like to report on today compared the effects of phenylpropanolamine (PPA) and d-amphetamine, a well-known appetite suppressant, on the feeding and reward-seeking behavior of rats.

Four rats in which the lateral hypothalamus was permanently implanted with an electrode and then electrically stimulated were used for the experiments. If food was present and the current turned on, a thoroughly satiated rat would immediately begin to eat and would continue to eat for as long as the current lasted.

By varying the rate at which these electrical pulses were presented, the number of pulses per second necessary to get the thoroughly satiated rats to begin eating within 20 seconds after the current was turned on was determined. Next, the number of pulses necessary when rats were pretreated with doses of PPA ranging from 0.82 to 33.0 mg/kg was determined.

At doses of 16.5 and 33.0 mg/kg, PPA markedly increased the number of pulses per second required to induce the rats to begin eating, thereby demonstrating the effectiveness of PPA as an appetite suppressant.

Whether or not PPA induces euphorogenic effects that might lead to the development of drug dependency was evaluated in the same four rats. Rats will voluntarily press down a lever to self-administer brief bursts of current to the reward system that runs through the same lateral hypothalamic region involved in controlling the appetite. Thus, by varying the rate at which electrical pulses of a constant intensity were presented, it was possible to vary the sense of reward. By arranging it so that each time a rat pressed the lever he obtained a 0.25-second train of pulses, it was possible to determine how many pulses in this train it would take to reward the rat enough to press the lever at least 20 times a minute.

The effect of PPA on the number of pulses required was determined using the same dose range and methodology as in the tests of appetite suppression. It was found that the number of pulses required to be rewarding did not decrease as the dose of PPA increased and may have actually increased slightly. This demonstrates that PPA has no ability to provide a reward, in contrast to d-amphetamine. When the rats were treated with d-amphetamine, the amount of current required for rewarding was greatly decreased, indicating that d-amphetamine was providing much of the reward itself. In the appetite suppressant tests, d-amphetamine greatly increased the amount of current necessary to elicit eating, confirming its appetite suppressant properties.

It was concluded that while d-amphetamine markedly suppressed appetite at doses even lower than those required for PPA, it also markedly potentiated reward, perhaps even to a euphoric level. In contrast, no dose of PPA tested potentiated reward, although PPA, like d-amphetamine, decreased appetite.

These findings are in agreement with the studies conducted by Prof. Bartley G. Hoebel of Princeton University in both rats and humans, which found that PPA was an effective appetite suppressant with no euphorogenic properties. In his human studies, which were published in 1975 in the journal *Obesity and Bariatric Medicine*, Hoebel did not observe any stimulant or other adverse effects in the subjects.

In conclusion, based on my own studies and similar studies by Hoebel, phenylpropanolamine is an effective appetite suppressant that does not induce any central nervous system stimulation or euphorogenic effects.

I ask that my comments and a copy of the study I discussed be entered into the record.

Thank you.

Coons, E. E. Exhibit

A. Hoebel, B. G. et al., Body Weight Decreased in Humans By Phenylpropanolamine Taken Before Meals, Obesity/Bariatric Med. Vol. 4, No. 5, 1975

Bartley G. Hoebel,[1] Iseli K. Krauss,[1] Joel Cooper[1] and David Willard[2]

Body Weight Decreased in Humans By Phenylpropanolamine Taken Before Meals

In a double-blind, subject-crossover study, phenylpropanolamine (propadrine, PPA) taken as sold over the counter reduced body weight in 70 adults significantly more than a placebo pill. During the first two weeks, both the subjects taking the placebo and those taking phenylpropanolamine lost weight, but during the second two weeks only those taking the drug continued to lose ($p<0.01$). On daily questionnaires, those taking the drug reported no change in the way they felt or the time it took to fall asleep. They did report a significant reduction in supper size and in the total number of snacks taken. When subjects took the placebo, they reported a significantly greater number of large afternoon and evening snacks than when taking phenylpropanolamine. It is concluded that this drug, which is structurally similar to catecholamines and amphetamine, can cause a perceived decrease in food intake and reduce body weight without noticeable stimulatory side effects.

The present study was undertaken as part of a series of studies to investigate the effectiveness of phenylpropanolamine in appetite suppression and weight control. This drug, also known as norephedrine, is an amphetamine analogue that causes little or no psychomotor stimulation.[1] It has the same structure as amphetamine but with an hydroxyl group on the beta carbon atom which makes it more like norepinephrine. It is a vasoconstrictor and is marketed in most nasal decongestants.[2] Handbooks which aid doctors in choosing drugs point out that even though this drug is commonly sold as an anorectic, there has been no convincing evidence that it is effective.[3,4] There have been no well-controlled studies although several case studies indicate some effect. The reader is referred to Silverman[5] for a review of phenylpropanolamine and to Hoebel[6] for a review of the pharmacology of feeding.

Studies with animals demonstrated that this drug is much less stimulating than amphetamine. In comparison it did not increase oxygen consumption[7] and did not appear to increase activity level as much as amphetamine even though it effectively suppressed appetite in rats as shown by Epstein[8] and unpublished work in our laboratory. It does, however, increase activity level in stabilimeter cages. Daily injections of the drug reduced feeding and chronically reduced body weight according to our unpublished data. We found it selectively inhibited feeding, but not drinking, elicited by electrical stimulation of the hypothalamus.[9] Moreover, it depressed hypothalamic self-stimulation whereas amphetamine had the opposite effect.[9] Thus, animal studies suggested this drug is an effective appetite suppressant without disruptive psychomotor stimulation. The next question was whether or not phenylpro-

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[1] From the department of psychology, Princeton University.

[2] From the Medical Center at Princeton.

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panolamine would also suppress food intake in humans leading to weight loss without noticeable psychomotor stimulation.

Previous studies carried out by this laboratory with volunteer human subjects who were concerned with their weight showed that phenylpropanolamine taken 30 minutes before lunch in a double-blind study reduced lunch size.[10] This suggested that taken before every meal the drug would cause weight loss. A pilot study with 30 volunteers indicated that when taken as directed on the commercial package, phenylpropanolamine caused a significant weight loss not matched in subjects taking a placebo similar in appearance but containing no active ingredients.[11]

The current experiment was designed as a larger scale study of the effect of phenylpropanolamine on weight loss in a double-blind crossover experiment with seventy subjects, each serving as his or her own control. We found that phenylpropanolamine can cause a statistically significant weight loss.

Method

Subjects. Subjects were volunteers from the Princeton area who answered an advertisement for people interested in their weight. Each prospective subject was told that this was a medically supervised, scientific study involving an over the counter, nonprescription appetite suppressant and a placebo. It was explained that they would receive each pill half the time, but that they would not be told when they were given one or the other. They were further told that each person who completed the study would receive $20.00 and a month's supply of pills if they wanted it at the end of the study. Following an examination by the physician for evidence of heart condition, high blood pressure, thyroid disease, diabetes or other conditions for which use of phenylpropanolamine might possibly be contraindicated, each volunteer was given a blood test (SMA, CBS + DIFF, T_4 by radioassay) which was analyzed by the laboratory of the Medical Center at Princeton. Seventy persons, 50 females and 20 males, were accepted by the physician and subsequently completed the study. A description of the study population by age and weight is found in Table I. The weight range information for each subject was determined with the use of the Desirable Weight Range table found in the Statistical Bulletin of the Metropolitan Life Insurance Company, Volume 40, November-December, 1959. As can be seen in Table I, two subjects fell below their desirable weight range according to the Metropolitan table and eight fell within their desirable range. All other subjects were above their desirable range. The ages of the subjects ranged from 18 to 64, the initial weights from 113 to 281 pounds.

Table I: Distribution of Subjects by Age, Sex and Weight Range (N=70)

	Group		
	Phenylpropanolamine Placebo	Placebo Phenylpropanolamine	Total
Age			
18-20	6	3	9
21-30	14	16	30
31-40	5	5	10
41-50	7	6	13
51-65	2	6	8
			N=70
Weight Range			
Underweight	0	2	2
Within desirable weight range	6	2	8
.1-15 pounds overweight	10	15	25
15.1-25 pounds overweight	8	7	15
25.1 pounds overweight and above	10	10	20
			N=70
Sex			
Male	8	12	20
Female	26	24	50
			N=70

Procedure. Each subject received phenylpropanolamine hydrochloride* during the two weeks of the study and the placebo for two weeks. The subjects were randomly assigned to either the drug-placebo order of testing (two weeks of phenylpropanolamine followed by two weeks of placebo) or the placebo-drug order (placebo followed by the drug). The order was counterbalanced so that about half the subjects had the drug first and the other half had placebo first. The assignments were accomplished in two steps. The principal investigator assigned subject numbers to conditions, and the technicians assigned the numbers to the subjects in the order in which they appeared on the first day of the study. The technicians did not know which subjects were assigned to which condition or even how many conditions there were. The subjects knew only their assigned numbers and that by the end of the study they would have taken each pill half the time. No special diets were prescribed or suggested. The subjects were requested to arrive at the study office each weekday for four weeks at approximately the same time of day to be weighed by one of three technicians and to receive a vial of three pills, one of which was to be taken a half hour before each meal.

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* *Hungrex*, Alleghany Pharmacal Corp.

Pills were provided by the manufacturer in the form as sold over the counter (25 mg) except that the placebos contained no phenylpropanolamine. All pills were placed in clear gelatin capsules so there would be no difference in appearance or taste. The principal investigator placed the capsules containing either phenylpropanolamine pills or placebo pills into vials, three per vial, which were labeled with the subjects' numbers and the day the capsules were to be taken. The technicians were responsible for seeing that each subject was given the proper vial each day. On weekends or other brief holidays subjects were given two or three dated vials of capsules, enough to last until their next appointment at the laboratory.

All subjects were also requested to fill out two questionnaires daily, the first of which described what was eaten at each meal, the time each pill was taken, the subjects' perception of the size of the meal relative to their typical meal size and the occurrence of snacks and their size. The second questionnaire was designed to provide information on physical symptoms experienced each day and sleep patterns.

On the final day of the study numerous anthropomorphic measurements were taken of each subject for future reference, and a final weight was recorded. The principal investigator or the supervisor informed each subject how much weight he or she had lost or gained with the placebo and with the drug without revealing the pattern of pill distribution. The subjects were given $[illegible]0.00 and, if they wished, a month's supply of the drug.

Results

The mean body weights for each weighing for all subjects are shown graphically in Figure 1. It is evident from Figure 1 that in the first two-week period (left half of the figure) both the subjects taking phenylpropanolamine and those taking the placebo lost weight, but those taking the drug

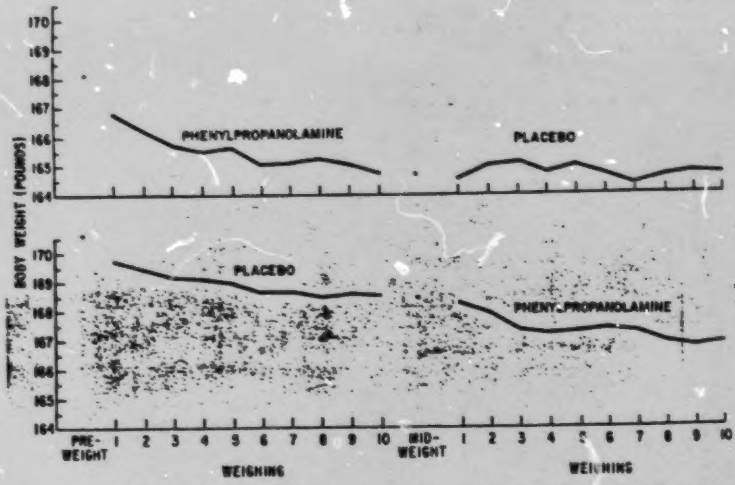

Figure 1: Subjects (top line) taking phenylpropanolamine for two weeks followed by placebo for two weeks lost weight with the drug and gained weight with placebo. Subjects (bottom line) taking the placebo first lost weight during both periods. Values are given for the ten weighings in each two week period (i.e., no weighings on weekends).

Table II: Mean Body Weight at the Beginning (First Weight) and at the End (Tenth Weight) of Each Two Week Test Period. Each Subject Took Phenylpropanolamine before Meals for One Period and a Placebo for the Other Period. Net Change in Body Weight and Percent of Body Weight Loss Are Also Shown.

Group	First Two Weeks				Second Two Weeks			
	First Weight lbs.	Tenth Weight lbs.	Change lbs.	Percent Wgt. Change %	First Weight lbs.	Tenth Weight lbs.	Change lbs.	Percent Wgt. Change %
Drug— 1st 2 wks. Placebo— 2nd 2 wks. N=34	166.78	164.77	−2.01	−1.2	164.54	164.70	+0.16	+0.2
Placebo— 1st 2 wks. Drug— 2nd 2 wks. N=36	169.74	168.51	−1.23	−0.7	168.27	166.87	−1.40	−0.8

appear to have lost more weight. In the second two-week period, shown on the right side of Figure 1, only those people who took the drug show a loss in weight. Weight on the day when subjects were switched from one condition to the other (midweight) is not included in the calculations.

Table II summarizes the mean weight of subjects at the beginning and end of each two-week test. People taking the drug the first two weeks lost an average of 2.01 pounds, then gained back 0.16 pounds on placebo. The other group of people who had placebo first, lost 1.23 pounds and then lost 1.40 pounds with the drug. Combining the two groups without regard for which pill came first, the 70 subjects lost 1.7 pounds with the drug and 0.54 pounds with the placebo. This is shown in Figure 2 as a mean percent weight change.

An analysis of variance was performed on the percentages of weight lost during each drug administration period. That is, for each subject we calculated the percent loss (or gain) relative to the initial weighing of that drug administration period. In the first period the

$$\%\ \text{weight change} = \frac{\text{weight (day 10)} - \text{weight (day 1)}}{\text{weight (day 1)}}.$$

Likewise, in the second period,

$$\%\ \text{weight change} = \frac{\text{weight (day 21)} - \text{weight (day 12)}}{\text{weight (day 12)}}.$$

The percent body weight change for both groups appears in Table II. The analysis of variance in Table III shows that the percent weight loss attributable to phenylpropanolamine is statistically reliable ($F = 12.75$, $p < 0.001$), but that the loss due to this drug was different for the two groups depending on which pill they had first. This finding was confirmed by a significant drug by group interaction ($F = 8.90$, $p < 0.01$).

Within the first two-week time period, both groups lost weight although the group taking phenylpropanolamine during that period lost more (phenylpropanolamine, 1.2% weight loss vs.

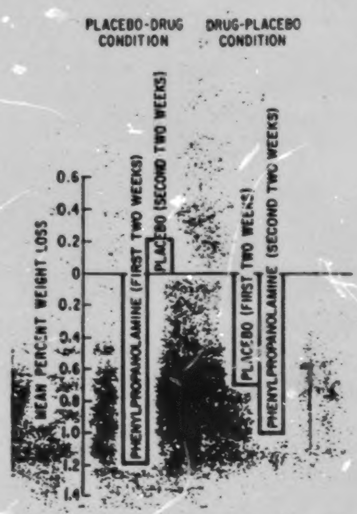

Figure 2: Percent weight change from the starting weight showing that phenylpropanolamine and placebo are both associated with weight loss the first two weeks, but the drug-induced weight loss is greater (left hand bar in each pair) and only the drug caused weight loss the second two weeks (right hand bar in each pair).

Table III: Analysis of Variance of Mean Percent Weight Losses

Source of Variation	df	Mean Square	F
Group (Drug-Placebo vs Placebo-Drug): A	1	.002 × 10^{-2}	0.75
Error	68	[illegible] × 10^{-2}	
Pill: B	1	.304 × 10^{-2}	12.78**
A × B	1	.142 × 10^{-2}	8.90*
Error	68	.016 × 10^{-2}	

* p<.01
** p<.001

placebo 0.7%). Post hoc comparisons (Sheffe method) of these mean losses indicated that the difference was not statistically reliable (F (1,68) = 2.71, p>.05). However this comparison between the mean percent weight loss of the two groups during the second two-week period (phenylpropanolamine 0.9% weight loss vs. placebo 0.2% weight gain) was significant (F (1,68) = 13.10, p<.05).

Over the entire month of study, a greater total loss occurred for the placebo-drug group (overall 2.63 pounds, a 1.6% loss) because the other group, drug-placebo, (overall 1.85 pounds, 1.0% loss) actually gained a small amount of weight during the time they were receiving the placebo. Figure 3 shows the overall effect of phenylpropanolamine vs. placebo in terms of per cent weight loss, whereas Figure 2 depicts the effectiveness of phenylpropanolamine in producing weight loss for each order of drug administration. When sex was added to the previous analysis as another variable, there were no significant differences in weight loss between men and women.

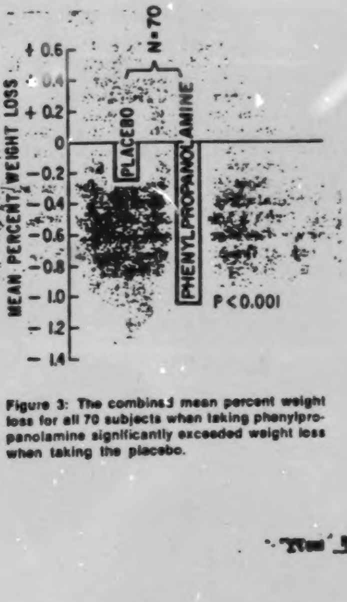

Figure 3: The combined mean percent weight loss for all 70 subjects when taking phenylpropanolamine significantly exceeded weight loss when taking the placebo.

Summarizing this body-weight data, it is clear that the placebo had a strong effect in the first two week phase of the experiment. Close examination of Figure 1 shows that there was even a decrease in weight between the time the subjects were first weighed during the doctor's examination (preweight) and the first day pills were administered a few days later. Thus the subjects' anticipation contributed to weight loss: both a placebo effect and the drug caused a weight loss during the first two weeks of the study, but only the drug caused a weight loss during the second two weeks and this effect was significant.

The subjective data on ease of getting to sleep and energy levels were analyzed by a matched pairs *t*-test of 35 subjects who reported at least once that it took more time than usual to fall asleep the previous night. The mean number of such responses while taking phenylpropanolamine was 1.71 and while taking the placebo, 2.09. The mean difference was not found to be significant. The corresponding means for the 35 subjects who recorded at least once that it took less time than usual to fall asleep at night were 2.14 for the drug and 2.43 for the placebo. The mean difference was not significant. Thus phenylpropanolamine did not affect perceived ease of falling asleep.

Similar results were found in the analysis of energy-level data. The mean number of reports for those 33 subjects reporting at least once that they had less energy than usual in the last 24 hours was 2.61 for phenylpropanolamine and 2.61 for the placebo, i.e. no difference at all. For the 32 subjects reporting more energy in the previous 24 hours the mean number of such daily responses for the drug was 1.69, for the placebo 1.50, again not significant. These results show that this drug did not affect sleeping habits or energy levels any differently than did the placebo.

On the question which asked if subjects noticed any unusual tastes or feeling, there were so few responses of any kind that an analysis was not attempted.

The subjects' personal records of meals, snacks and whether they ate less, the same, or more than usual at each meal proved very interesting. Each of the significant results in Table IV was in the direction one would expect for an effective appe-

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Table IV: Mean Number of "Less than Usual" and "More than Usual" Responses for Meals and Snacks, and Total Number of Snacks

	N	Mean Responses for Drug	Mean Responses for Placebo	Mean Difference	t	Level of Signif.
Responded "Ate less than usual":						
Breakfast	49	4.08	4.12	−.04	−0.11	NS
AM snack	39	3.51	2.92	.59	1.21	NS
Lunch	60	4.10	3.73	.37	1.23	NS
PM snack	46	3.67	3.17	.50	1.15	NS
Supper	59	3.71*	2.71	1.00	2.66	.005
Evening snack	49	3.45	2.90	.55	1.33	NS
Total meals and snacks	70	16.49*	14.00	2.49	2.8[illegible]	.01
Responded "Ate more than usual":						
Breakfast	56	1.50	1.77	−.27	−0.97	NS
AM snack	29	1.86	1.86	.00	.00	NS
Lunch	51	2.02	2.43	−.41	1.29	NS
PM snack	47	1.47	1.98*	−.51	2.11	.025
Supper	57	2.25	2.60	−.35	1.54	NS
Evening snack	59	2.31	2.77*	−.46	1.86	.05
Total meals and snacks	70	8.09	9.67*	−1.58	2.50	.01
Total number of snacks regardless of size:						
	88	14.93	16.31*	−1.38	−1.99	.05

*Statistically significant

tite suppressant. For example, there were significantly more responses of "ate *less* than usual" for supper for people on the drug than on placebo. Conversely, in the "ate *more* than usual" category, afternoon and evening snacks were indicated more often by people on placebo than people on the drug. Also revealing is the total number of snacks reported. Subjects taking the drug reported a mean of 14.9 snacks. When taking placebo they reported 16.3 snacks ($t = 1.99$, $p < 0.05$). Thus, judging by the subjects' own reports of food intake, we would conclude that the reason they lost more weight with the drug than with placebo was because they ate less, particularly at supper, and they cut down on the size and frequency of afternoon and evening snacks.

Discussion

Insurance company statistics have shown that people live longer if they keep their weight down to the young adult level,[12] and some medical experts maintain that even a transient weight loss to give the heart a rest can be beneficial as noted at the Ciba-Geigy Conference on Obesity: The Human Energy Crisis, 1973. Therefore, a drug which causes weight loss by curbing food intake without notable side effects might be a valuable medication for some overweight people.

The side effects of this drug seem to be minimal to the extent one can judge from the subjective reports we collected daily. The drug is marketed widely as a nasal decongestant, and it can affect blood pressure although this effect is relatively minor.[1] Now that we have demonstrated a behavioral effect in the form of decreased food intake[10] with a loss of body weight as shown here, one wonders if any other behavior systems are affected. At the present time there seem to be no studies looking for any influence on thirst, sex or other basic behavior patterns in humans. Several studies report no evidence that the drug is a stimulant at the dose tested.[5]

If subjects can detect side effects, there is always a possibility in human experiments of this type that they give results due to their expectations which they then label as side effects.[3] The effect we observed for phenylpropanolamine would seem to be reasonably specific because there was no effect on the subjective reports of feelings or energy level even though there was a weight loss. Similarly, in our studies of lunch size, the subjects ate less on drug days but generally did not report feeling any different when they filled out the questionnaires immediately after the meal. Therefore, we assume that the subjects' expectations were properly accounted for by the placebo control procedures and within-subject comparisons built into this study.

One should also be aware that our evidence for a statistically significant weight loss in a two-week period does not mean that this rate of loss would be continued over longer periods. Drug tolerance and a myriad of other physiological and social factors could affect longer term results.

Both the pilot study and the present study showed a statistically significant weight loss with phenylpropanolamine. Statistical significance does not necessarily imply medical significance; doctors can judge whether or not the average weight losses reported here are worthwhile. In our two-week pilot study with 30 subjects, 15 on phenylpropanolamine and 15 on placebo, the phenylpropanolamine subjects lost weight, 3.8 pounds, and the placebo subjects did not. In the present study with 70 subjects, all of whom had both phenylpropanolamine and placebo tests, the subjects lost about one pound in anticipation of the study, another one or two pounds in the first two weeks depending on whether they had the placebo or the drug, and a third pound in the second two weeks if they had the drug. There was an indication that the drug started working the first day; the mean weight for people who started taking the drug was significantly lower the second day than the first and this was not true for people who started on the placebo. The overall results show that phenylpropanolamine (25 mg) can on the average cause at least some weight loss and this, of course, means that some individuals might lose many pounds and others not at all. Given our positive results and the fact that most people by far do not find this drug to be a stimulant, it is reasonable to suggest that this is a drug of choice in a doctor's search for an appetite suppressant that is medically useful for some overweight patients.

In conclusion, this study repeats on a larger scale the basic finding of our prior study and demonstrates conclusively that phenylpropanolamine can cause a statistically significant weight loss in people who take it as directed on the package. Specifically, we found the following: 1) The 70 subjects in this experiment lost weight significantly over a two-week period when they took phenylpropanolamine compared to a placebo; 2) they reported no feelings of altered energy level and found falling asleep no more or less easy than usual; 3) their food intake was significantly affected according to their own reports. When taking phenylpropanolamine the subjects reported eating smaller suppers and fewer snacks.

These data therefore demonstrate that phenylpropanolamine was effective in producing a short-term weight loss in the population sampled. They further suggest that weight loss was accomplished, at least in part, by a decrease in food intake. ▣

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Ms. OAKAR. Thank you very much.

Dr. SILVERMAN. Thank you, Professor Coons. Now, if we could have the committee's indulgence and even though they have no preprepared statements, I would like to ask if it would be appropriate, and I would gladly give up my seat if the three consumers could come to the front and present their own testimony.

Ms. OAKAR. What I would like to do first is have the committee ask questions first and then have the witnesses, and we'll ask questions.

Dr. SILVERMAN. Of course.

Ms. OAKAR. Mr. Lantos?

Mr. LANTOS. Thank you, Madam Chairman.

Dr. Winick, I was very much impressed by your testimony, and there is just one item I'd like to explore with you. Did I hear you correctly that 101 substances were more frequent in their appearance?

Dr. WINICK. Yes, sir, that's correct.

Mr. LANTOS. Could you expand on that study a bit, because I find it startling?

Dr. WINICK. The Drug Abuse Warning Network, Mr. Lantos, is the country's most broad-based and representative program to collect information on overdoses, accidents with drugs, and so forth. It's unlike the poison control report, which was a one-shot and covered a finite period of time. The emergency rooms that report to DAWN, which is an agency jointly sponsored by the DEA and NIDA, do so on a regular basis. They report all emergencies that come to them. And the results are analyzed on a quarterly basis and they have been published now for 10 years. In the most recent one, which covers the third quarter of 1982, of the many substances listed, 101 were more frequently cited than PPA, and PPA accounted for .017, less than one-fifth of 1 percent of all of those mentioned.

Mr. LANTOS. I hope my next question is not an unfair one. How many of the 101 substances which appeared more frequently have been ruled off the market?

Dr. WINICK. Well, some of them, of course, are illegal substances, such as heroin. They're not available at all.

Mr. LANTOS. Yes.

Dr. WINICK. So that includes many substances which either are illegal or, like cocaine, which may have an accepted medical use but which are used for mood modification in an illegal manner.

Mr. LANTOS. Are there any of the 101 which appeared more frequently which are not illegal that have been taken off the market?

Dr. WINICK. No, not to my knowledge.

Mr. LANTOS. So what you are suggesting is that substances which appear more frequently in the DAWN study are on the market?

Dr. WINICK. Very much so; yes.

Mr. LANTOS. Very much on the market. Could you give us examples, any of you gentlemen, of these substances, any of these substances?

Dr. WINICK. No.

Mr. LANTOS. For a layman it's fascinating to observe why the onslaught on PPA when apparently there are dramatically more dangerous substances, and many of them, which are freely being sold.

Dr. Winick. Well, for example, there are many barbiturates on the list, caffeine, for example, is number 90 in terms of mentions. Aspirin is number 50. In other words, there are a number of widely-used substances that are much more frequently cited than PPA.

Mr. Lantos. I have a question, if I may, Madam Chairman, to Dr. Coons. As I take it, your testimony is that rats don't read the newspapers and do not watch television, therefore, are not influenced by the manipulation of the advertising agencies.

Dr. Coons. Well, they're innocent of media influence, I trust.

Mr. Lantos. You think they're innocent of media influence?

Assuming that that is correct, could you expand on that study? Because I find that a great deal of the earlier testimony focused on deceptive advertising, and that is why people take these, and that is why we have such a problem.

Dr. Coons. Well, we have a phenomena that is known as the placebo effect. It's often—it often has very good properties; that is, it's a psychological effect: A person thinks they're getting a drug and they aren't; they're getting a sugar pill, but they go ahead and do very well. Then, however, there are people who think they're getting a drug who have some other psychological reaction to the drug, which is really a sugar pill, and have a bad effect.

So, what you have to do to get around that is to test in animals and, as I said before, they're innocent of these kinds of influences, of preconceptions of what a drug might do for them or fears they might harbor about a drug. Thus, you can look at the outcome of a drug treatment in animals, with appropriate controls, as bearing a great deal of weight in telling what the true effect of the drug is, over and above the placebo effect or, in other words, the powers of suggestion.

Mr. Lantos. I have one final question, if I may, Madam Chairman.

It's not unusual for professionals in various disciplines, even economists, to disagree. And we have heard physicians who have taken a point of view different from what we have heard lately. I would like to get a general statement from each of you if I may, whether on balance it is your view that the products we are discussing here are harmful or helpful to the American public.

Dr. Silverman. Well, let me start off and let me say as firmly and as convincingly as I can that the products that we are discussing; that is, the OTC products in general—and phenylpropanolamine specifically—are safe, they're efficacious, and in my opinion as a professor of pharmacy, for upward of 30 years, there's no question but what the American public is receiving are safe and efficacious OTC medicines, very helpful medicines.

In point of fact, and something that was not yet mentioned during today's review and hearing, is that not just one, not just two, but actually three FDA review panels have reviewed phenylpropanolamine specifically from the standpoint of safety, beginning with the cough and cold panel, whose monograph was published in 1976; the weight control monograph, which was published in 1982; and a monograph also published in 1982, which always seems to get lost in the cracks, but which reports on the and use of phenylpropanolamine in the oral cavity, finding phenylpropanolamine to be safe.

Three separate expert panels found phenylpropanolamine to be safe, three independent expert panels working at different periods of time over a period of approximately 7 years, with the latest monograph published only in May 1982. PPA is a very safe and a very efficacious drug. Of this I am absolutely convinced.

Dr. **Coons**. Well, human research is not my specialty so I would, again, address myself to the rats and say that I think that PPA, in the——

Ms. **Oakar**. There is a similarity?

Dr. **Coons**. Yes. In the doses that I've administered in my study, which went from half the normal dose up to 20 times the normal dose equivalent for humans, was safe. These were in normal tensive rats, not the rats that are hypertensive-prone, as you heard from Dr. Mueller. So, that's my contribution.

Unidentified Voice. Several years ago, just about 25 years ago, I was an anesthesiologist and I have learned, I believed, quite a bit about medicine because I was dealing with life and death every day. I left anesthesiology voluntarily because my first love was to treat obese individuals, and they always remind me of that song, you know, laughing on the outside and crying on the inside, and I have done everything in my power to try to help these people and they do need help.

The amphetamines were taken off the market because of abuse. They were excellent appetite depressants. Search has continued since then, and I was involved with the research work for finding a way that we could help these people, keeping in mind that obesity, it's a complex medical disease, and that you need to treat not just with medications.

I was very happy to contribute to the research work on phenylpropanolamine because I found that it is an adjunct, a very valuable adjunct, in my practice. This morning we were talking about blood pressure, and so on. There are still many doctors that will not give a medication to a patient who happens to be obese and has high blood pressure, and yet there are people that need these medications, and I have found that blood pressure actually comes down because of the improved health. That's the benefit that you get by losing the weight.

But again, you treat the individual who happens to have the disease, and not just the disease. And this is why I hope that I will be given the privilege to continue to use phenylpropanolamine, along with other modalities, in my practice, and I hope that that day will never come when I will have to give that up.

Thank you.

Dr. **Bradley**. As stated by Dr. Conte, and we've heard a great deal of testimony today that the obese hypertensive is at great risk with this drug, on the exact opposite side I would say the obese hypertensive is in most need of losing weight, because as a person loses weight his blood pressure tends to normalize.

In my study, I entered into this study because I felt a great need for this type of medicine and to date I have seen no side effects, I have seen no aggravation of hypertension. I think this is a very important thing. I am very much in favor of this medicine.

Dr. **Silverman**. Before Dr. Winick continues, may I just comment, so that it is properly highlighted, on the study of Dr. Bradley, Dr. Bradley deliberately used hypertensives and it's continuously said that only healthy people are ever evaluated, when PPA is tested. Now, this study was specifically done to evaluate just what is the effect of PPA on the general population.

Dr. Winick?

Dr. **Winick**. I would like to say that having looked at the literature on the effectiveness of PPA in weight reduction, there is no doubt in my mind, first of all, that the accepted criteria for conducting such studies have been followed. There is a standard way of doing medical research with a comparison group and using accepted, conventional statistical procedures.

Every one of these studies involve the use of exactly the kind of methodology that would be taught in a class on the conduct of social or medical research, and the data accumulated, it seems to me, are quite overwhelming in terms of demonstrating, certainly, effectiveness and safety.

In terms of the other side of the coin, the hazards that have been alluded to, my studies of epidemiology which have been conducted by and for agencies of the Federal Government, foundations, State agencies, and concerned citizens, certainly have led me to conclude that there is no hazard of abuse here, this is not a gateway drug, it doesn't lead to other drugs, other drugs don't lead to it, and so forth, and it seems to me that evaluating the very clear and consistent demonstration of effectiveness which involve the application of established procedures and evaluating the nonexistent risk of abuse that the situation is a clear one.

In terms of the nonpublication in the journal, let me just say that the International Journal of Obesity is one of the world's leading journals in the field It's relatively new and perhaps that's why it's not as well known to some persons as it might be. It is a refereed journal with peer review and it's edited by a very distinguished scholar in California, a medical scientist connected with a medical school with an internationally distinguished board of advisory editors. It perhaps might be well just to make that explicit.

Dr. **Noble**. Ms. Oakar, gentlemen of the panel, in the next 1 minute—60 seconds—let me summarize for you my 15 years experience in treating overweight patients, first as codirector of the Obesity Clinic of the University of California, and subsequently as director of my own private clinic in San Francisco. First of all, I think I've seen about 10,000 patients, and with the exception of Dr. Conte, I don't think anyone has seen as many patients as perhaps he and I have. I think he's seen about 10,000, too.

So, I think we are in a position to talk about real experience. These are people who come to us wanting to lose weight. We're not talking about rats or what one has read in some Australian or faraway journal.

First point, of these 10,000 patients, I can count only on 1 hand—maybe 2—patients over age 70. So, I would say to you, don't worry about the elderly rushing out and getting diet pills. For some reason, they're happy they're 70 and they want to stay where they are and they don't want to lose weight in general.

Ms. **Oakar**. What about people who are over 50 or 60?

Dr. NOBLE. Yes, definitely more in these groups.

Ms. OAKAR. You have to be worried about them.

Dr. NOBLE. Yes, but I'd say 70, very few. There are some who are 50 and some who are 60. The number seems to go down after that.

Now, with respect to the efficacy of phenylpropanolamine.

Mr. LANTOS. Couldn't you find an easier name so we can all pronounce it?

Dr. NOBLE. I'm sorry. PPA.

You know, it would be really great if, as a doctor, a patient comes to me seeking to lose weight if I could merely say, "get out there and try willpower and just cut down your calories." That would be marvelous. But you have no idea how many patients have tried this a thousand times before.

They come to the doctor and they want him to give them something. All right? So what do I give him? I have to give him something. I find that phenylpropanolamine is just as good as anything by prescription. So why not give them phenylpropanolamine and save them all the problems and cost, specially if there are no side effects?

The second point: How safe is phenylpropanolamine? I think perhaps I've studied phenylpropanolamine more than any other person in this country at the clinical level. I would say I have seen and tested now, in double-blind, well-controlled studies about 1,000 patients. These are very restrictive studies and we have to report them to an institutional review board. We have to be totally impartial. I have tested under these conditions about a thousand patients, I would say 600 on obesity and 400 on cough/cold preparations. I have yet to find one side effect that really shook me up, with one exception.

Let me tell you about this. In that 216-patient study that I just talked to you about, which was a 12-hour study. I'm addressing this to some of these people who, quote-unquote, "Were victimized by PPA."

Patients in this 12-hour study could have received as much as 75 milligrams of PPA. Everything went fine. However, one patient went home and at 4 o'clock the next day she called me saying, "Oh, my God, Doctor, I've got severe chest pains, my whole left side is paralyzed, I'm short of breath, I've got this ringing noise in my ears, I can't even hear you on the telephone, I've got a headache, get over here."

I said, "Oh, my Lord, what have I done now? Did PPA do this?" I rush over there. She was sort of a beatnik living in sort of beatnik conditions. She looked fine to me but she said, "Doctor, I see butterflies jumping up and down across the dresser. Don't you see them?" I said, "No, I don't see them." I examined her and found her physical state to be normal.

I went back and under emergency conditions I broke the code to see what she had been getting on the study the previous day. Lo and behold, she was getting placebo, a dummy pill. Now, are we going to ban placebos because they cause hallucinations, chest pains, and all these weird things that this patient was complaining about?

All I'm saying is that when you are dealing with a product that's as common as PPA, there are going to be various reports of oddball things happening, and it would be unfair to blame it all on PPA because if you delve and probe, I daresay with most of these victims today you might well find alternative causes.

Thank you very much.

Dr. **Silverman**. We might add that a placebo is a sugar pill, an inert pill. It has no activity whatsoever.

Ms. **Oakar**. And you're saying that all of you, in your testing, use placebos and the patients did not know that they were getting placebos?

Dr. **Noble**. Absolutely.

Ms. **Oakar**. Are you going to say that for the record?

Dr. **Funderburk**. That's called a double blind study.

Ms. **Oakar**. Right. Every single one of you is going to say that? Will you say it, from Johns Hopkins?

Dr. **Bradley**. It's all controlled, it's all coded, we cannot look at what is given, we have to be impartial, and at the end of the study then they finally tell us who got what.

Dr. **Funderburk**. I can speak to that from a statistical point of view and an experimental design point of view. The way the studies that we conducted at Hopkins and that Dr. Noble conducted and that all of us at this table have conducted have been conducted under what are called double blind conditions. The drugs are packaged by an independent party in identical capsules of identical shape and appearance. There is no way in which to tell which is the active drug product and which is the placebo.

The patients are administered the medication under identical conditions and all the experimental procedures are the same for all the patients in the study.

There is absolutely no way for an investigator to know what the patients are getting. The data are submitted by the investigators to the sponsor or whoever is going to do the statistical analysis of the data and at that point, when the data are in hand, the code is broken and the statistical analysis proceeds.

Once the statistical analysis is completed, then you have the completed report, which is then given back to the investigator, the statistical report, for his clinical evaluation of the results. And that's the way the studies have been done. All the studies that are listed here were conducted using appropriate scientific methodology and just to comment a bit further on a point that Dr. Silverman made, there have been a large number of studies conducted under double blind conditions, well-controlled, clinical evaluations of phenylpropanolamine, at recommended doses, and the evidence is just overwhelming in terms of the absence of side effects, and the efficacy of the product.

Dr. **Silverman**. Thank you, Mr. Funderburk. Dr. Sebok?

Dr. **Sebok**. Overweight people most of the time, if they are not sick, are overweight because they eat too much. Most of them will not admit it. They don't even realize it. So, if we give them PPA before meals and they unconsciously learn better eating habits and are not hungry and will eat less, this will help them for the future to keep up the good eating habits.

We don't expect them to keep it up forever. The aim is to use PPA as a crutch to help them to learn better eating habits. Certainly, either the doctor or the person himself has to realize, whether he is a candidate to take PPA or not. Sick people should not take it.

Ms. **Oakar**. Thank you. Thank you very much.

Dr. **Funderburk**. Thank you, Madam Chairman.

Dr. **Silverman**. I realize it's late but could I ask the committee's indulgence for an afterthought by my good colleague, Dr. Coons?

Ms. **Oakar**. No, I'm sorry to say. My colleague has questions, I have questions, and we should have been out of the room at 1 o'clock. We also want to hear from your other witnesses. So, let's proceed.

Mr. Bilirakis?

Mr. **Bilirakis**. Thank you, Madam Chairman.

Well, I came to this hearing principally because I was concerned with the misuse of the over-the-counter-type drugs by the elderly. And I'm still concerned with that.

Obviously, I think that misuse of any drugs on the part of anybody is of concern, and we should meritoriously be prepared to tackle those types of problems. But I haven't heard that much testimony in terms of the adverse effect on the elderly, which is my biggest concern. I guess the entire hearing has evolved into an attack on—an onslaught, as Mr. Lantos very ably put it—on PPA. If PPA is dangerous, then so be it. We should be concerned about that too, because it's going to affect the elderly as well as the rest of the population.

I would ask Dr. Bradley just very quickly, since he comes from an area similar to mine, I am from the Tampa Bay area, sir, with about 50 percent of my district being elderly. In the studies that you referred to, sir, about how many elderly were included in those patients?

Dr. **Bradley**. Our protocol allows for up to 874. That's been approved by the Research Committee of the Miami Heart Institute, and the Human Subjects Committee. Our oldest patient so far has been 70. We've had another of 67. I have an older population that I have to choose from. So, they have been in the forties, fifties, sixties, and seventies, one aged 70.

Mr. **Bilirakis**. Dr. Winick, would you have any opinion, sir, in terms of the percentage of people who take PPA, which are in the elderly category?

Dr. **Winick**. Well, everything that I know, sir, is that it's a relatively small proportion of the user population, and if you look at, say, the text of magazines like Modern Maturity or Fifty Plus, even though there is, of course, an enormous amount of material on health, and on eating well, there's relatively little on diet pills or various medications to help oneself to eat less, and if we look at the data from DAWN and other sources, of difficulties that people have had, the senior citizen population is very, very small, consistently small. So, my sense is that, A, it's a relatively small proportion of the user population that involves seniors, and that they are, therefore, underrepresented, and if they take it, they are less likely to get into difficulties than younger persons, contrary to what has been said about them in general, in terms of these substances.

[The following material was subsequently received from Dr. Winick:]

This statement is submitted for the record of the House Select Committee on Aging, Subcommittee on Health and Long-Term Care, to supplement my remarks at the July 21, 1983 Hearings on Drug Misuse and the Elderly, and in response to matters raised during the Hearings. I shall deal with the epidemiology of phenylpropanolamine (PPA) use as it involves the older user.

EPIDEMIOLOGY OF PHENYLPROPANOLAMINE USE BY OLDER PERSONS

All available data, from survey, marketing, observational and treatment sources indicate that senior citizens, defined as persons aged 60 or more, seldom takes appetite suppressants. For most of the senior (60+), or elderly (65–75), or old (75+) population, the kinds of cosmetic or asthetic appearance considerations which may be important in earlier periods of the life cycle are far less salient. The comments below summarize my observations, in a naturalistic market situation, on the phenylpropanolamine purchasing behavior of a substantial sample of consumers; two different analyses which I conducted of phenylpropanolamine consumer response forms; and a summary of industry practice with respect to selling phenylpropanolamine products to persons over 60. The studies of my own which are cited below were conducted for other purposes, but it has been possible to analyze the age data for purposes of this submission.

The three studies which are summarized below clearly indicate that the use of phenylpropanolamine is so minimal that it cannot be eligible to be considered a health hazard to senior citizens.

1. Observations of consumers purchasing phenylpropanolamine products: During 1976 and 1977, I observed over one thousand persons shopping for appetite suppressants in discount stores, drug stores, and other retail establishments selling these products in the Metropolitan New York area. A sample of these consumers was then approached in order to make arrangements for a personal interview, to be conducted in their homes, at their convenience.

My field notes of the total population observed (n = 1,053) indicates that 11 percent were between 50 and 59 years old, in terms of their estimated age. There were three purchasers aged 60 or more, or .3 percent. Since these observations were conducted over a period of many weeks, their validity would appear to be high. I have used similar techniques of visual assessment of demographic characteristics of consumers in studies sponsored by the National Science Foundation and a Presidential Commission. [1]

2. Two different analyses of consumer response forms: I have conducted two different analyses of reports of consumer experiences with phenylpropanolamine products. In 1975, I studied a 100 percent sample of the 3,245 package inserts submitted to Thompson Medical Company by purchasers of its appetite suppressants containing phenylpropanolamine in 1972 and 1983. [2] These inserts included information on how long the product had been used, the outcome of its use, and demographic information, including age.

In 1977, I similarly analyzed all of the 422 inserts received from phenylpropanolamine users during a five week period in April-May 1975. [3]

For the 1972–73 sample, the average age of the consumers was 31.8 and .6 percent of the users were 60 or over. For the 1975 sample, the average age was 31.5 and .5 percent of the users aged 60 or over. The 60 plus age group accounts for about 12 percent of the population. So that, with less than one percent actually buying the product, senior citizens represent minimal users of phenylpropanolamine products. Put another way, persons over 60 are extremely underrepresented among phenylpropanolamine users.

3. Industry practice with respect to selling phenylpropanolamine products in persons over 60: A content analysis of all the advertisements in the two leading magazines for senior (Modern Maturity and 50-Plus) for the period 1978–81 found that there was not even one advertisement for appetite suppressants in these publications. This study was conducted as part of a Ph.D. thesis on media images of the aging. [4] The appetite suppressant industry clearly does not promote these products to senior citizens.

Thompson Medical Company has, on all of its phenylpropanolamine appetite suppressants, the statement, in bold face type, that the product should not be used by persons "Under the age of 18 or over 60 except under the advice and supervision of a physician."

The industry is not advertising its products to senior citizens and Thompson Medical Company actively discourages persons over 60 from buying them. Since the studies cited earlier indicate that senior citizens represent minimal users of phenylpropanolamine appetite suppressants, and since the industry advises senior citizens not to buy these products, there would seem to be a minimal public health hazard posed by senior citizens' use of these products.

REFERENCES

1. C. Winick, Some Observations on Characteristics of Patrons of Adult Theaters and Bookstores, in Volume IV, Technical Report of the Commission on Obscenity and Pornogaphy. Washington: Government Printing Office, 1971, 225-244.
2. C. Winick, Two Consumer Studies and a Report on Abuse Potential of Phenlpropanolamine. Submitted to the Food and Drug Administration July, 1977.
3. Ibid.
4. B.C. Loetterle, Media Images of the Aging. Ph.D. Thesis, Department of Sociology, City University of New York, 1983.

Mr. BILIRAKIS. Of course, since they are more likely to misuse the drugs as a result of not being able to understand the labels, or not bothering to read the labels, or any of the other problems that result from being elderly, or their eating habits being somewhat different. I'm certainly not belittling, Madam Chairman, the need for this type of a hearing as it involves our elderly.

Ms. OAKAR. Right.

Mr. BILIRAKIS. I'm just trying to get to tbe proper perspective in terms of percentages.

Ms. OAKAR. Well, if you'll yield, I have already indicated that I will submit for the record the number of complaints that FDA has gotten. It is a computerized list and 30 percent of them are over 55. Maybe you don't consider that older Americans. We have had some disability hearings where our witnesses were 30 years old. But nonetheless, you know, statistically in terms of the complaints and the numbers who have called the poison control center, which is part of FDA, consistently it's a tremendous number of older Americans. So this is an appropriate committee to conduct it.

But even if it weren't, should we not be concerned about those under 55?

Mr. BILIRAKIS. Yes. Well, I've made that comment.

Ms. OAKAR. Right.

Mr. BILIRAKIS. And I certainly think that we should be concerned. I don't like the age 55 level, quite frankly, because I'm fast approaching it. I'd like to raise that, maybe, by a few years.

I understand tbat PPA has been on the market for better than 40 years. Is that correct?

Dr. SILVERMAN. Approximately 50 years.

Mr. BILIRAKIS. Approximately 50 years. Has it been under attack, under the onslaught, going back to Mr. Lantos' word, for that period of time?

Dr. SILVERMAN. No, it has not been.

Mr. BILIRAKIS. It's just a recent thing?

Dr. SILVERMAN. I think only within the recent past few years that it has received a tremendous onslaught of attack. Up to this time, and now, phenylpropanolamine has been freely available in any pharmacy, and as a pharmacist I can go back to the time I went to college. It never was a prescription medication. It always was an over-the-counter medication. You can purchase it in your pharmacy today under the original brand name, of Propadrine.

If this drug were used, for example, promiscuously, as has been suggested by some other witnesses, the pharmacist could never stock the original product on his shelves. For all intents and pur-

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poses, it is not used promiscuously. Neither is it abused. And Dr. Winick testified to that.

The drug has received critiques, if you will, only within the last, oh, perhaps 4, perhaps 5, years. But the studies that have been reported are not controlled studies. They are anecdotal, case report type. Invariably the study will turn out to be either a deliberate overdose, where a person ingested a handful of capsules, or ingested a deliberate overdose in combination with alcohol, or took, as one of the earlier witnesses testified today, a polypharmaceutical type of preparation where phenylpropanolamine was combined, for example, with an antihistaminic.

Antihistaminics are well known to evidence bizarre reactions in humans when taken in overdose.

PPA has been under attack, if you will, only in the last few years. The number of safety studies on PPA go back to the time it was first brought out onto the market, and that was in the late 1930's. It has been studied in animals since that time and it never would have been brought onto the market in the first place, released by the FDA, if you will, if it were not a safe drug.

While the FDA, in 1962, I think, after the Kefauver bill was passed, required new drugs to show both safety and efficacy, up to that time a drug would appear on the market only if it were safe. The fact that phenylpropanolamine was marketed, as well as many, many other drugs before that time, indicated without question that FDA had reviewed it from the standpoint of safety.

From the standpoint of efficacy, in the last several years and going even beyond that, dozens of studies, well nigh 50-odd studies, have now been completed, showing phenylpropanolamine as an efficacious drug. And I believe that none of the witnesses who preceded this panel testified or indicated that phenylpropanolamine was not efficacious. They all said it was efficacious. It would cause a decrease in appetite.

And if the question of safety has arisen, it is only because of anecdotal studies. And if the question of safety is pointed out in terms of a so-called controlled study, that study, completed in Australia, was not done in this country and was used with a so-called phenylpropanolamine which was never identified as the same drug—and let me use a tongue twister—the same stereoisomer, the same actual phenylpropanolamine, that is used in this country.

You can take this chemical and produce approximately eight different modifications of it. Some modifications have greater effect; some have a lesser effect.

The product that was used in Australia, from at least the package indication, showed it to be a phenylpropanolamine of a different stereoisometric characteristic.

Mr. **Bilirakis**. But Dr. Silverman, with an answer somewhat briefer than this last one, I wonder, could you tell us very quickly why do you think, that PPA—and I'll continue to use the simpler term—has been under attack during these last 3 to 4 years? Why is it under attack now?

Dr. **Silverman**. I can offer a speculation. I believe it has been under attack because, for whatever reason, there has been the promiscuous promotion of this product in combination with caffeine and ephedrine as a so-called high drug. Mail order promotion has hurt a lot of legitimate drugs. This preparation has been under attack because of the so-called look alike problem which is still not yet controlled.

I can, and I have done this, purchased through mail order, preparations containing phenylpropanolamine and caffeine, both of which are in overdose. In other words, the tablets contained more PPA and more caffeine than are permitted by law.

This is where the real problem is and this, I would submit to the committee, with all due respect, is where the attention should be placed. If you can stop the mail order promoters from promoting the illicit, illegal use of the stimulant effect of these look alikes, the problem, as we think we believe it to be a problem, will vanish.

Mr. BILIRAKIS. Very good. Dr. Coons, I know you're very anxious to comment.

Dr. COONS. Oh, yes. I just want to comment, again, on the placebo effect. Where you have a look alike, you are going to have an act alike. Just by the powers of suggestion. And this is precisely where animal studies are extremely important. My rats showed that there was absolutely no euphoric or high effect of phenylpropanolamine.

PPA is chemically related to dexedrine. But whereas dexedrine, or d-amphetamine, produces a great high in rats, phenylpropanolamine emphatically does not. If anything, it does slightly the opposite.

Mr. BILIRAKIS. It sounds like our attention, maybe, should be focused to the look alikes and the transportables.

Dr. SILVERMAN. As a scientist who has been an academician for upwards of 30 years and has spent his career teaching pharmacy students and medical students, there is a real problem with mail orders. There is a real problem with look alikes, and I believe—I think it was Dr. Schwartz who said that the smaller companies are really not paid attention to. The bigger companies are. By careful regulation of the smaller companies, the problems as we think we perceive them will vanish. There is no problem in the American marketplace today with the responsible and correct use of anorectic preparations.

Ms. OAKAR. Thank you.

Mr. BILIRAKIS. Thank you.

Ms. OAKAR. Let me ask a few questions. First of all, PPA did not meet any safety test before 1962 because it was exempted and came on the market before the Food and Drug Act.

Dr. SILVERMAN. Ms. Oakar, I'm sorry to interrupt you but there were several safety tests that were done on PPA before 1962.

Ms. OAKAR. It was never approved by FDA in any way, shape, or form. It still isn't.

Dr. SILVERMAN. It never would have been released and never would have been placed onto the market without testing for safety.

Ms. OAKAR. That's one of the reasons we wanted FDA here. We wanted to ask FDA why it allowed this drug on the market? Why aren't you asking the same questions that victims, like the 61-year-old woman who testified she had a stroke asked? She didn't order that pill through the mail, although we had the Post Office testify. That woman took a very well known product and bought it in a drugstore.

Dr. **Silverman**. But what we don't know is whether or not that person was taking any other kind of medication.

Ms. **Oakar**. We asked that and she said she was in perfect health. All of the victims, and we purposely tried to select people who had no other medical problems at the time, were healthy.

Let me ask all of you, and I think it's an important question, have you been, in any way, paid by the industry for your services?

Dr. **Silverman**. I'll start that off. I've done a lot of studies on phenylpropanolamine. The first study I did on phenylpropanolamine nobody paid me. I was a poor struggling academician. I did what I thought was ivory towered research. I still do what I believe is ivory towered research.

The study I did required me to work considerably to find volunteers. It took an awful lot of time, an awful lot of sweat, and required me to, in terms of time, months to do a study that with a little bit of support I could have completed very, very quickly.

Ms. **Oakar**. Are you paid by the industry?

Dr. **Silverman**. Yes, I am. But only from the standpoint of having the study supported. That's all. We're talking about expenses.

Ms. **Oakar**. That's all right. That's fair. I understand it. I know it's hard.

Is there anybody who is not paid by the industry on this?

Dr. **Conte**. Madam Chairman, may I say that I have done other studies for other companies and I don't say I got paid. They gave a grant and out of that grant I have to pay the laboratory, I have to pay the nurses in my office, I have to pay the rent, and of course for my time. But, the thing that is important to me, and I'm a clinician, I am not going to use something that I don't know anything about.

Ms. **Oakar**. That's right.

Dr. **Conte**. And I'm not going to continue to use something that is going to hurt my patients. Because it is just counterproductive.

Ms. **Oakar**. And most patients who buy over-the-counter drugs don't have access to a doctor.

Dr. **Conte**. OK.

Ms. **Oakar**. They don't go to a doctor to tell them whether or not to buy diet drugs.

Dr. **Conte**. Right.

Ms. **Oakar**. They go to you. They're lucky if they have your constant care.

Dr. **Conte**. Wonderful, but——

Ms. **Oakar**. That's very atypical.

Dr. **Conte**. But why did I do this study?

Ms. **Oakar**. That's right.

Dr. **Conte**. Because as a physician I also have the responsibility to the people that live in my area. You know in——

Ms. **Oakar**. My mother is from your hometown. Beaver, Pa. That's a beautiful area.

Dr. **Conte**. Do you know where Boardman is, Boardman, Ohio?

Ms. **Oakar**. I sure do. It's wonderful. It's great.

Dr. **Conte**. I happen to have another place over there. But—

Ms. **Oakar**. But let me ask the question again. Is there anybody who hasn't been paid by the industry? You have not been paid?

Dr. BRADLEY. Of course we get paid. We have our overhead and all our expenses.

Ms. OAKAR. Oh, I see.

Dr. BRADLEY. But one thing I want to point out. We don't get paid on how the results come out. I've done a lot of clinical studies and I would say 60 percent come out negative for the drug company. They're highly impartial.

Ms. OAKAR. And here's the problem, not just with this drug. The drug companies have the opportunity to submit whatever studies they want. They don't have to submit the studies that don't prove, the way they want them to come out.

Dr. SILVERMAN. Up to a point. Let me comment on that, please. Up to a point. With the initiation of the institutional review boards and the review by peer review committees of all studies that are done by internists, by clinicians, whenever human patients are involved, the FDA is aware of what studies are ongoing and what happens with the results. It's an open book. It's an actual open book.

Ms. OAKAR. That's why we wanted them to be here today, because we wanted to ask the FDA how they could possibly allow this kind of thing.

Dr. COONS. I would like to make a comment too. I was asked by Thompson to run this study on rats, to doublecheck on——

Ms. OAKAR. Did you get paid?

Dr. COONS. I got the expenses for doing the study, that is, buying the rats and, you know, research is expensive. I had that. But I was asked to do this to check on some other studies that have been done by Professor Hoebel at Princeton. He has done studies on PPA in rats and in humans.

Ms. OAKAR. Right.

Dr. COONS. And it was a doublecheck. And I must say that I would be very foolish professionally to do anything that was not going to be correct, and as a scientist I certainly wouldn't.

Mr. BILIRAKIS. Would the gentlelady yield a moment?

Ms. OAKAR. I'll be happy to yield, briefly.

Mr. BILIRAKIS. Briefly, yes.

I accept what these gentlemen say in the same spirit, in the same sense of credibility, as I accepted what the previous witnesses said.

Ms. OAKAR. But there's a major difference, though. The previous witnesses are not paid by the drug company.

Mr. BILIRAKIS. Well, they weren't paid by the drug companies.

Ms. OAKAR. Yes.

Mr. BILIRAKIS. I have attended hearing after hearing after hearing with this Aging Committee and other committees, and I assure you that someone selects these particular witnesses for what they are going to testify to. It isn't a matter of reaching out and grabbing somebody off the street, not knowing what they are going to testify to.

Ms. OAKAR. That's correct.

Mr. BILIRAKIS. So, there isn't complete objectivity in any particular area.

I doubt very much that—excuse me, ma'am—I doubt very much if the gentleman testifying from the Johns Hopkins School of Medicine, for instance, or some of these other universities, are going to testify falsely or in some, unilateral way. I think that their reputation is certainly good—I don't think they need any defense on my part. But I think I had to say that.

I've had the same feeling, sometimes, regarding some of the witnesses that we have had up here who have been hand picked by whomever, certainly not by this side of the aisle, and this should not be a partisan type of a thing.

Ms. **Oakar**. It sure isn't. Not when people are really in terrible shape.

Mr. **Bilirakis**. Yes, but there have been hand picked witnesses.

Ms. **Oakar**. Let me read from the Federal Register. They still haven't made any definitive regulations or come out with a final draft or monograph. But this is from February 26, 1982, which you refer to Dr. Silverman. Some of you indicated that you even give PPA to heart patients who have high blood pressure. Am I correct about that?

Well, let me refer to the Register, which several of you have mentioned kind of proves that they concluded that it was safe and effective:

> PPA by obese persons with hypertension may significantly increase their risk of heart attacks, stroke, and kidney failure, and considering the positive association between hypertensive and obesity, the increase in risk becomes very evident because obese people are most likely to use weight control products.

They further conclude that in the studies that were reported to them, with only using 50 milligrams of PPA, and most often it's 75, 11 percent of the subjects given one single dose of 50 milligrams developed hypertension and a single dose of 85 milligrams in a time-released product caused hypertension—sometimes severe—in 32 to 33 percent. And what is fascinating to me is when you read the body of the Register you really get alarmed. And then you read the conclusion. I wanted to ask FDA, did somebody else write the conclusion? Because surely what is in the body of this Register does not match the conclusion.

Now, a conclusion, from my old English teacher days, is supposed to either summarize what's in the body of this prepared prelude to a monograph or it's supposed to form some conclusion based on what's in the body of the material. I can't, for the life of me, figure out who wrote the conclusion because the body of it is a lot different.

Furthermore, you stated——

Dr. **Silverman**. May I comment on that, Ms. Oakar?

Ms. **Oakar**. Surely.

Dr. **Silverman**. May I very shortly, very briefly?

Ms. **Oakar**. Sure.

Dr. **Silverman**. Because I'm pleased to indicate to the panel that at least one of my studies has been written up in that preamble that you just described. What that preamble indicates is that it alludes or describes anecdotal studies, the studies that we have discussed over and over again today, a few patients, one patient, and so forth. And what the FDA did, and I consult for the FDA also, what the FDA did was ask the drug industry, if you will, as well as investigators, whomever they might be, to carry out safety studies, do more studies, and this is one of the reasons why we're here.

Areas discussed today represent newer studies that have been submitted and these investigators with whom I have come today have carried out some of these studies.

Indeed, Dr. Bradley's studies done on hypertensives were done in response, in partial response, to this request.

Ms. **Oakar**. To this study?

Dr. **Silverman**. Yes.

Ms. **Oakar**. Let me comment on the fact that we talked about what you call this new onslaught of PPA. It's really not new—the numbers of cases are reported year by year. We've changed our attitude toward alcohol. We've changed our attitude toward the manner in which cigarettes are promoted in this country. We've forced labels to be readable. That's only happened in the last few years. And we certainly have changed our attitude toward other drugs.

My own feeling, obviously, is that these over-the-counter drugs leave a lot to be desired, that the advertising is hyperbolized.

For example, in California there is a case that the attorney general won, that was settled out of court. You mentioned that it's not a stimulant. Our books from the Library of Congress call it a stimulant. In California it's mandated, am I correct, that you call it a stimulant, because California won that case and settled out of court? But in Washington, D.C., you don't have to do that. Why did they settle out of court if it's not a stimulant? Why did they settle out of court with the individual who was a victim of the stroke today?

Dr. **Silverman**. I don't know why the company settled out of court, because I am not a lawyer and neither am I competent enough to be able to provide you any type of an intelligent statement in reply to your question. But as far as its being a stimulant, Dr. Schwartz, who was not part of this panel, I think, provided us with the answer. He said that many chemicals have similar structural resemblances, but they have different pharmacological effects.

The reason why PPA is classified as a so-called stimulant is because it is structurally related to the amphetamines. But it is not an amphetamine inducer in terms of its pharmacological effect.

Now, Dr. Schwartz, who I believe appeared at the invitation of this committee, indicated that to you earlier. And I would respectfully say that the studies that have been sponsored by industry validate that statement that it is not a stimulant. The studies at Johns Hopkins have indicated that it is not a stimulant, and these studies were done in the lower animal, the primate, as well as in the human.

Ms. **Oakar**. Let me thank the panel. I think what we're trying to do is arrive at—what I'm trying to do, is protect the consumer. I'm here to protect the consumer. And if that means that we keep safe and decent drugs on the market, that's what we need. We realize the contributions of certain drugs. We also know that 66 percent of all over-the-counter drugs are not safe or effective.

I would like to briefly ask your people here, who all look fairly trim, to come up, if they'd like, and say just a few words. The other committee wanted to be in here an hour ago, so the chairman is going to really be disturbed.

Dr. Bradley, I meant to ask you and I forgot to, for the record, how many people you used in your hypertensive study?

Dr. **Bradley**. Well, because we were concerned about all of this information on hypertension, we did a pilot study of 10 patients.

Ms. **Oakar**. Ten People?

Dr. **Bradley**. Correct. Now we've started on another study of 60, of which I have completed 28.

Ms. **Oakar**. I see. They don't have low blood pressure, do they?

Dr. **Bradley**. No, no, they have to have high blood pressure. It's part of the protocol.

Ms. **Oakar**. I see. Would you like to briefly introduce your people?

Dr. **Silverman**. Let me briefly introduce the consumers, Ms. Barbara Ritz, Mr. James Schreiber, Sr., and Mr. James Schreiber, Jr.

Ms. **Oakar**. Right. We'll have time for you to make a statement. OK?

STATEMENT OF JAMES SCHREIBER, JR.

Mr. **Schreiber, Jr.** My name is James Schreiber and I was 19 years old when I tried the product Dexatrim. I weighed about 235 pounds—no, 230 pounds, 225, 230. And I had a 38- to 40-inch waist. I took the product and it worked. It suppressed my appetite. The rest was up to me, to keep a good diet and to maintain it. And in 3 months I lost about 60 pounds. In the next couple of months I lost 25 more pounds and dropped 85 pounds altogether. And I cut my waist size down to 32 and I now weigh 155, approximately.

Ms. **Oakar**. You look good.

Mr. **Schreiber, Jr.** Thank you.

And I've kept the weight off, going on 2½ years. I never felt high from the product. I really don't believe you can feel high from that.

Ms. **Oakar**. Did you feel nervous?

Mr. **Schreiber, Jr.** Never. Now, but I'm not on the product.

Ms. **Oakar**. Right now. Are you being paid by the drug industry?

Mr. **Schreiber, Jr.** I've never been paid.

Ms. **Oakar**. Never been paid?

Mr. **Schreiber, Jr.** No.

Ms. **Oakar**. Totally voluntary. Well, that's good.

Would your father like to say a few words for the committee? Because we really are forced to get out of the room and I apologize about that.

Mr. **Schreiber, Sr.** Yes, I know.

STATEMENT OF JAMES SCHREIBER, SR.

James Schreiber, Sr. I am assistant professor at Trenton State College in Trenton. What my son says is correct. It's hard to believe that he did weigh 230 pounds. I weighed about 185 pounds and after seeing him lose the weight I decided to try it. I lost about 20 pounds, from 185 to 165, and as a 45-year-old man I was particularly worried about high blood pressure and side effects, and I can honestly testify I had none, none whatsoever.

Ms. **Oakar**. Great. How about you?

STATEMENT OF BARBARA RITZ

Ms. RITZ. Hi. I'm Barbara Ritz. At age 40 I weighed approximately 160 pounds and I was in great danger of high blood pressure and, I was told, a candidate for a stroke. A member of the family is a physician. He told me to take the Dexatrim. He said, "Barbara, it's easier to get that weight down and get yourself under control by taking the Dexatrim rather than being that much overweight and having to worry about a stroke."

I took the Dexatrim. I did not have any adverse reactions I feel better. I'm like a new person. And I have no blood pressure problems at all right now.

Ms. OAKAR. None of you have ever been paid in any way?

Ms. RITZ. No. No. Not at all. Do you have any questions for us?

Ms. OAKAR. Good. Great.

Mr. LANTOS. How much do you weigh now?

Ms. RITZ. 110 pounds.

Mr. LANTOS. So you dropped 50?

Ms. RITZ. Yes.

Mr. LANTOS. Fifty-some pounds.

Ms. RITZ. Yes, in 20 weeks.

Ms. OAKAR. You are a lot luckier than the other witnesses who took pills—they had hypertension, cerebral hemorrhages and strokes, and permanent damage from ingesting the pills in prescribed dosages.

Thank you all for being here today. I sincerely hope that Congress takes action and sees that over-the-counter diet pills containing PPA, which is neither effective nor safe, are taken off the market—or at the very least—that they are made prescription drugs. And especially, I call on my colleagues to think about consumers and their need and rights to be protected.

I would like to thank staff members of the subcommittee and my office for their dedicated and hard work in preparing for this hearing. I especially appreciate Millie Vinicour, who identified this issue and oversaw all of the groundwork, Daniel Rosenblum an extraordinary intern, who assisted in the extensive analytical efforts, and Nancy LeaMond, who drafted proposed legislation to improve the performance of the Food and Drug Administration.

[Whereupon, a 2 p.m., the hearing was adjourned.]

APPENDIX 1

ST. PETERSBURG TIMES ■ MONDAY, JULY 18, 1983 5B

Survey finds more than half of Pinellas elderly misusing medicine

By PAT PORTER
St. Petersburg Times Staff Writer

More than half the people age 60 and older surveyed by a Pinellas County drug program were taking their medicine in a potentially dangerous manner.

The survey by Operation PAR (Parental Awareness and Responsibility) indicated that elderly persons engage in a variety of unsafe medication practices. They include using old prescriptions, sharing prescriptions with friends and taking over-the-counter drugs at the same time they take prescriptions, without consulting a doctor.

Although PAR is known for its work concerning drug problems among young people, PAR has operated a program for the elderly since 1979 because of concern about drug misuse by the elderly.

PAR conducted the survey in March and April. A questionnaire was given to 270 respondents at congregate dining centers and at county day care centers. A shorter questionnaire was administered to 86 persons at the Senior Citizen Showcase of Services.

THE LARGE amount of medicine the elderly take is a basic cause of the problem.

The survey showed that the elderly use a disproportionate amount of both prescription and over-the-counter drugs. This increases the risks that arise from the combination of drugs, which can result in effects that neither drug alone would cause.

Just two weeks ago at a joint meeting of the U.S. Senate and House aging committees, witnesses told about physical and mental side effects that elderly persons have experienced from the misuse of drugs, including false signs of irreversible senility. Actually, the problem was excessively high doses of medications.

Mary Ann Morck, PAR program evaluator and author of the local group's report, said young people need to be reminded that "Grandma could be a little slow (or unusually animated) because her medicine is messing her up."

According to the report on the survey, "Medication Use/Abuse Among the Pinellas County Elderly," people 60 and older make up 9 percent of the national population but purchase 25 percent of all prescription drugs. The report said the elderly are 35 percent of the population in Pinellas County.

Of the respondents to the survey, 98.4% were consumers of prescription medicine. Ms. Morck said any elderly person who takes more than two medications more than once a day is especially at risk. The number of different prescriptions and the number of times they are taken contribute to the potential for misuse.

ELDERLY PERSONS generally do not like to take drugs unless they have to. When they are ill they tend to search for over-the-counter drugs instead of going to the doctor, said Dr. Lou Salerno, PAR Community Education Director.

The misuse of over-the-counter drugs is one of the biggest problems. Some elderly patients take too many, or take the wrong kind or, most seriously, take over-the-counter drugs along with prescription medicines without consulting a doctor about this multitude of medicines. More than 40 percent of the respondents said they never consulted their doctor when using over-the-counter drugs with prescriptions; 30 percent said they sometimes did.

The report listed frequently used over-the-counter drugs that can be hazardous to the elderly: painkillers, laxatives, diuretics, vitamins, antacids and cough medicines.

Doctor-shopping contributes significantly to the problem of misuse. The elderly, Ms. Morck said, often have more than one ailment and will go from doctor to doctor, getting a different prescription from each. A patient often fails to tell each doctor what other doctors have prescribed and what over-the-counter medicines the patient is taking. The doctor might then unknowingly prescribe a medicine that will interact with the other drugs to cause side effects.

Ms. Morck emphasized the need for communication between elderly persons and their doctors. She said when a doctor prescribes medicine, an elderly person should fully inform the doctor of all the drugs the patient is taking, including "that little shot of whiskey or those two glasses of wine taken at night as a home remedy."

Ms. Morck said most of the research by drug companies about drug effects has concerned younger people, but the effects of drugs in the elderly can be quite different from those in younger patients.

AGE AFFECTS the rate at which drugs are metabolized in the body and how quickly they are eliminated. Also, she said, older people generally eat less than younger people do.

The eating habits of older persons can cause complications. "Suppose," Ms. Morck said, "the doctor tells the patient to take two pills after meals, thinking the patient eats three regular meals a day. This can be a very difficult or confusing schedule for a patient who does not eat three times a day (or) eats very little when he does eat."

PAR's educational presentations, made by Salerno, encourage good record-keeping by the elderly and communication with health care professionals and with family members who are caring for them.

Salerno said he will address "any group of people, any day of the week, day or night, for 15 minutes or three hours, whether there will be 10 people there or 10,000."

In addition to lectures, PAR will provide any elderly person a free booklet called "Passport to Good Health Care" in which a person can record the medicine he is taking; the schedule for use; the color, shape and strength of each drug, and the directions and warnings for each one.

PAR can be reached at 527-5866.

MEDICATION USE/ABUSE AMONG THE PINELLAS COUNTY ELDERLY

June 1983

Operation PAR, Inc.
Elder/Ed Program
6613 49th Street North
Pinellas Park, Florida
33565
(813)527-5866

Operation PAR is a comprehensive drug abuse education, prevention and treatment program. Drug misuse and abuse affects all age groups. Most drug abuse education, prevention and treatment programs traditionally have focused on adolescents and young adults. However, the problems of medication misuse among older Americans are serious and complex.

Medication is a valuable therapeutic tool for the care of the elderly. Research indicates that as a group, the elderly compose approximately 9% of the national population, yet consume approximately 25% of all prescribed drugs. In Pinellas County, the elderly constitute 34.9% of the total population. The relatively high rate of medication use in conjunction with the per cent of the total population along with the dysfunctional aspects of the aging process place the elderly "at risk" with respect to the potential misuse of prescription and over-the-counter medication.

In 1979, as a result of interest in drug mismanagement behaviors of the elderly, Operation PAR began the Elder/Ed Program. As the program developed, it became evident that no systematic attempt had been made to identify the medication/drug use needs of Pinellas County elderly. An initial survey was conducted to attempt to gain insight into the medication concerns and behaviors of the elderly. The survey was crude, but provided a basis for program development. In order to enhance Elder/Ed services and more accurately define the medication misuse needs of the elderly, Operation PAR redesigned the initial instrument to provide more comprehensive information into the medication practices of Pinellas County elderly.

Methodology

Measuring the severity of the medication misuse problem among the elderly is a complex task. The survey was designed to secure information regarding the demographic characteristics of the respondent, his/her general health, prescription drug use, as well as the use of over-the-counter medication. Two instruments were developed. The longer questionnaire included 35 questions and was administered to Neighborly Senior Service recipients. The total number of respondents (N) in this subgroup was 270. A shorter version was developed for use at the "Senior Citizen Showcase of Services." The total number of respondents (N) in this group was 85.

In order to make the survey as easy to complete as possible, all questions required a forced choice response. The forced choice format enabled participants to check the appropriate response with an option to explain a notation of "other". Both instruments were presented in large bold face type on brightly colored paper to ease any reading problems.

The target population was identified as Pinellas County residents 60 years of age or older. In order to develop a sample group representative of the population, three major subgroups were identified: 1)congregate dining recipients; 2) county day care clients; and 3)at-large respondents from the "Senior Citizens Showcase of Services." The congregate and day care respondents provided PAR with the opportunity to make brief introductory statements regarding the survey, then read through the instrument question by question. Average completion time was 15 minutes. The at large group surveyed at the Senior Citizen Showcase of Services presented a different administration concern. The Showcase is an annual day long informational forum showcasing elderly services available in Pinellas County. Generally, the Showcase provides information outreach to approximately 3,500 elderly citizens. The instrument for administration at the Showcase had to be concise with a completion time of between 1-3 minutes. The abbreviated version of the questionnaire included questions in all areas of interest that can be compared to the other subgroups.

There was a total of 356 survey participants. 57.9% (206) of the respondents were from the Neighborly Dining Program, 18.2% (65) of the participants were enrolled in the Adult Day Care Program, and 23.8%(85) completed surveys at the Showcase. According to information secured from the Tampa Bay Regional Planning Council, there were 7,317 recipients of dining services and 591 adults in day care during 1982. In light of these figures, PAR survey sampled approximately 3% of the congregate participants and 11.2% of the day care participants. Surveys were distributed at the Neighborly Senior Service Centers in conjunction with an Elder/Ed presentation. Staff was available to assist participants whose eyesight was insufficient to complete the survey. It is of note that several participants indicated an inability to read the survey, but were in total control of their medication.

Congregate and Day Care sites were chosen in order to attain a representative county-wide sample. The following sites were utilized in the survey sample:

Dining Program

St. Petersburg Beach Civic Hall
1500 Pass-A-Grille Way
St. Petersburg Beach

Mirror Lake Christian Church
737 3rd Avenue North
St. Petersburg

Rogate Lutheran Church
2447 East Bay Drive
Largo

Gulfport Presbyterian Church
4201 6th Street South
St. Petersburg

Mount Carmel Baptist Church
1014 Pennsylvania
Clearwater

Day Care

Lealman United Methodist Church
4090 58th Avenue North
St. Petersburg

Palm Harbor Day Care
1550 16th Street
Palm Harbor

Woodlawn Presbyterian Church
1235 26th Avenue North
St. Petersburg

Survey results will be reviewed by participant category and overall. Base data charts which include individual question tabulations can be found in the appendix. Results will be grouped according to the type of question: demographics; prescription drugs; over-the-counter medication; unsafe medication practices an "at risk" factors.

As a group, studies have shown that elderly consumption of medication is disproportionate to their percentage of the total population. Despite the relatively high rate of consumption, the elderly are hesitant to discuss drug use or misuse. There appears to be an inherent reluctance to identify medication as drugs. In the development of the survey, care was taken to use the term "medication" instead of "drug(s)" whenever possible to reduce the anxiety of the elderly respondent.

Additionally, it should be noted that as survey results are reported the total number of responses will vary. This variance is attributed to two major factors. Several questions are selective. An example is an inquiry as to whether the respondent uses prescription medication. A negative response would not require the respondent to answer additional questions regarding prescription medications. The second factor contributing to incomplete responses is the misconceptions that surround the elderly perception of drug use and the interest of others in their medicating behaviors. Overall, the response percentage was approximately 84.3%. This means that on an average, participants responded to 30 out of the 35 questions. Information regarding completion percentage per question is provided in Appendix B.

III. Profile of Survey Participants

The majority of individuals surveyed were women (60.1%). Approximately 7.6% of the respondents were non-white. The ages of respondents were fairly well distributed: 34.4% averaged 60-69; 39.3% averaged 70-79; and 26.3% averaged 80 and older. Most of the elderly surveyed lived alone (48.1%), only 2% resided in some form of group care. The variable of living alone can be considered a "risk" factor with regards to medication mismanagement.

76.1% of the individuals surveyed were participants in a county social service assistance program sponsored by Neighborly Senior Services. The remaining 23.9% were elderly who completed surveys at the Senior Citizens Showcase of Services. Additional information was secured regarding the respondents financial situation. Of the 356 respondents, 315 or 88.5% indicated receipt of Social Security benefits. 92 or 25.5% of the respondents cited receipt of multiple financial resources.

Respondents were asked if they considered themselves to be under regular care of a doctor. 76.2% of the Day Care respondents were under a doctor's care as compared to 63.8% of the congregate respondents. Comparative figures were not available from the "at-large" population. Overall, 66.8% of the elderly surveyed were under regular care by a doctor. The remaining 33.2% of the respondents not under regular doctor's care could respond to discomfort or minor illness with a self-medicating practice. This situation could place them "at risk" of medication misuse.

As stated previously, the elderly consume a disproportionate share of over-the-counter medication. Respondents were asked to indicate how many of a listing of common ailments they tend to suffer from regularly. Of the ten conditions presented for review, only three (arthritis, high blood pressure, and chest pain) were of the variety generally considered to require immediate or prolonged medical attention. The remaining seven were common somatic complaints ranging from headaches to gas/indigestion. Information was available from only the congregate and day care groups.

Frequencies can be viewed by percentage of the total complaints cited or by the frequency of the condition by the total number of resondents. Information was also available on multiple complaints. 200 or 73.8% of the respondents identified at least one complaint. 58.5% of those who cited complaints identified arthritis. The conditions in rank order by frequency of identification are as follows:

Rank	Condition	*% of Those Responding Who Cited Condition
1	Arthritis	58.5%
2	Colds	49.5%
3	Leg Cramps	48.5%
4	High Blood Pressure	45.5%
5	Gas/Indigestion	30.5%
6	Coughs	25.5%
7	Headaches	24.0%
8	Stomach Problems	19.5%
9	Flu	19.0%
10	Chest Pain	15.5%

*Percentages were figured by taking the percentage frequency of the condition of the total who responded.

The average respondent cited 3.4 different complaints.

Respondents were then asked to categorize their general health as either poor, fair, good or excellent. The Day Care respondents tended to depict their health in more negative terms than those at the congregate sites. In general, approximately 85.5% of the respondents cited their health as either fair or good. The extreme categories of poor and excellent accounted for only 5.2% and 9.3% respectively.

Frequency of doctor visits was fairly evenly distributed. The most frequently cited response was "twice a year" (33.0%). The second most frequent response was "other" (25.4%). Upon review of the "other" category, the responses were either "as needed", "when sick" or "quarterly."

Another gauge of the general health of the survey group was derived from self reported sick days in the past two months. The average number of sick days per respondent was 3.4 over the two month period.

The final demographic or descriptive information on respondents dealt with the use of prescription medicine. 68.4% of the respondents indicated current use of prescribed medicine.

The typical survey respondent was:

Female
Aged 70-79
Living alone
Receiving social security
Under regular doctor's care
Suffers from 3 somatic complaints (probably arthritis)
Considered their health "good"
Sees their doctor twice a year
Taking prescribed medicine.

IV. Prescription Drug Use

Nine survey questions dealt directly with prescription drug use. These questions begin to deal with the "at risk" dimension along with reviewing unsafe medicating practices. Additionally, most of the prescription drug questions were asked of all three subgroups.

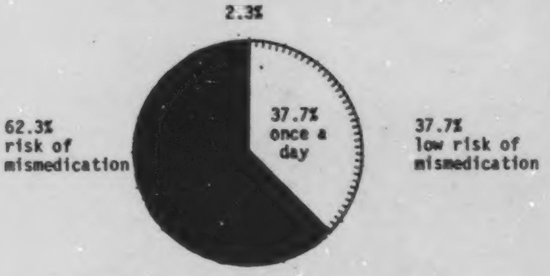
As stated previously 68.4% of all respondents take prescription medicine. Day care participants cited a higher percentage involvement with prescription medicine (78%) than congregate dining recipients (65.5%)

Prescription drug use for the elderly patient often involves multiple prescriptions and complicated medication schedules. Both the number of different medications used and the number of times medicated daily can heighten the risk potential for misuse. Survey participants were asked to cite the total number of different prescribed medications being utilized. The three subgroups reported significantly different results. 69.3% of the congregate dining participants citing prescription drug use, utilized from 1 - 2 different medications and 35.1% used 3 - 4 different medications. The day care clients cited 46.8% in the 1 - 2 category and 44.7% in the 3 - 4 medication category. Overall, 62% of those surveyed were taking 1 - 2 different prescription medications. With respect to risk, participants who indicated prescription drug use of three or more medications concurrently were considered "at risk". For the populations surveyed, 38% were considered "at risk" based upon the use of three of more different prescriptions.

A common condition associated with the aging process is forgetfullness and confusion. Complicated medication schedules create an additional "at risk" condition for the elderly patient. The more frequently a patient has to medicate, the higher the risk or error. In all of the subgroups, the majority of participants medicate two or more times daily. Overall, only 37.7% indicated a once a day medication schedule.

FIGURE 1

NUMBER OF TIMES MEDICATED DAILY



Combination of the number of prescribed medications taken and the frequency of medication yields a more in depth view of the medication practices of the elderly.

Risk with regards to the number of prescribed medications taken and medication schedules is defined as follows:

No/Low Risk

1 - 2 medications/once a day

Moderate Risk

1 - 2 medications/2 or more times daily
or
3 or more medications/once a day

High Risk

3 or more medications/2 or more times daily

Figure 2 displays the volume and percentage of cases by category. The figures indicate that approximately 67.2% of all respondents were at some level of risk with regards to the quantity of medication combined with a complicated medication schedule. The information is also beneficial with regards to program development. Over 89% of the respondents take between one and four medications between one and four times daily. Development of a dispensing aide would be most beneficial to this group. Extreme cases could be handled individually.

FIGURE 2

Cross-Classification Number of Different Medications Taken By The Times Medicated Daily

# of Diff. Meds.	# OF TIMES MEDICATED DAILY					
	1	2	3	4	5 OR MORE	TOTAL
1-2	81 32.7	40 16.1	25 10.1	13 5.2		159
3-4	10 4					62
5-6	1 .4					17
7-9						7
10 OR MORE	1 .4					3
TOTAL	93	64	54	32	5	248*

NO/LOW RISK: 32.7%
MODERATE RISK: 36.2%
HIGH RISK: 31.0%
*MISSING OBSERVATIONS = 12

*Percentages vary slightly from the tables in the appendix. The variance is due to the number of missing observations due to cross-classification.

Another factor that can increase the risk of medication misuse is the amount of different prescriptions on hand at home. Some prescriptions may no longer be used daily, but could be left over from acute illnesses. 69.4% of the participants indicated a supply of 1 to 3 different prescriptions at home. 11.2% indicated a total lack of prescriptions at home. The "at risk" group, 4 or more prescriptions on hand was 19.4% of those who responded.

An unsafe medication practice common to most people is discontinuance of medication if relief is perceived. This practice that appears on the surface to be innocuous to the general public can have serious effects upon the elderly. 21.3% of all survey participants admitted to discontinuing medication if (in their opinion) their health improved.

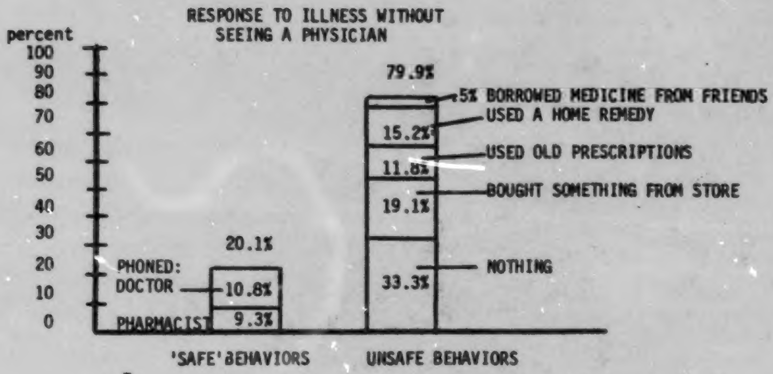
If a patient discontinues medication, the question then becomes what is done with any leftover medicine. 63.7% of the respondents indicated that leftover medicine was discarded. However, 34% admitted to saving leftover medicine for later use, and 2.3% indicated that they would share leftover medicines with others. Compiling a personal pharmacy and becoming a pharmacist to friends are unsafe behaviors, practiced by 36.3% of all survey participants.

Another common medication practice is self-diagnosis. Very often patients phone the doctor's office for a prescription rather than make an office visit. However, for the elderly patient this could be dangerous. Symptoms the elderly may recognize from the past might be new conditions brought about through the aging process. 42.9% of the respondents admitted phoning the doctor for a prescription.

It has been frequently cited that the elderly consume a disproportionate amount of medication. Additionally, as a group they have been acultured to rely on the judgement of doctors. However, most pharmacological research on drugs prescribed to the elderly is completed on much younger populations. A major concern of elderly serving professionals is whether or not the elderly client is aware of all the possible side effects of their medications. 34.1% of the respondents indicated no knowledge or understanding of the potential side effects of their daily medication. This lack of knowledge could lead to self-medication of a misdiagnosed side effect as a common non-serious ailment. Lack of knowledge of the potential side effects of medication is another "at risk" factor for the elderly.

The average American receives medical/pharmacology "training" daily through advertisements. The public is encouraged to review their symptomology, assuming the condition doesn't warrant a doctor's visit, and become their own diagnostician and pharmacist. Survey participants were asked to identify what they would do if they felt "sick" and didn't go to the doctor. The results of the forced choice responses are as follows:

FIGURE 3

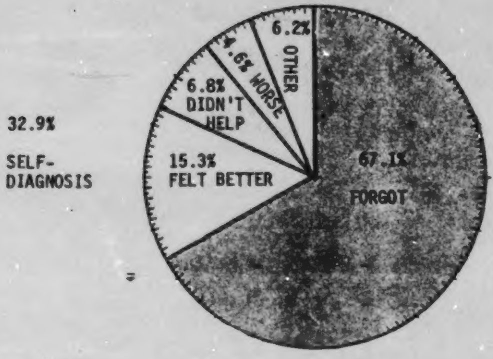


Only 9.3% of those surveyed indicated they might secure advice from a pharmacist. 10.8% indicated they would phone the doctor for a prescription. These two responses are the only responses that even attempted to involve a recognized medical practitioner. 79.9% of the survey participants involved themselves in some sort of self-diagnostic and prescribing behavior.

19.1% of those surveyed indicated that they would become involved with over-the-counter medication if ill. Use of over-the-counter medication is a common phenomena among the elderly. The following section will deal specifically with over-the-counter drug use among the elderly.

Probably the most common unsafe medication behavior ascribed to the elderly is failure to adhere to their medication schedule. Participants were asked if they ever missed taking their prescriptions. 41.6% indicated that they had missed self-medicating on at least one occasion. The reason behind missed medication was then explored. Participants were given five forced choice responses. Over 67.1% of all respondents indicated that they merely forgot. Three of the responses involved self-dianosis. 26.7% of the respondents identified involvement in self-dianostic behavior. 6.2% of the participants cited "other" reasons for missing medication. The predominant reason cited as "other" was that the prescription ran out.

FIGURE 4
REASONS CITED FOR MISSING
MEDICATION



Respondents were surveyed as to their response to an incident of missed medication. 74.8% indicated that they would wait until the next appropriate time to remedicate. However, 13.2% indicated that they would take another dose as soon as they realized the previous dose was missed. Immediate remedication is an unsafe behavior that frequently occurs among the elderly.

V. Over-The-Counter Medications

Another area of medication misuse among the elderly is inappropriate use of over-the-counter medications. 49.01% of the survey participants indicated use of over-the-counter drugs. Participants were also asked if they used over-the-counter drugs along with prescription medications. 44.5%

of the respondents indicated concurrent use of over-the-counter drugs and prescribed medications.

Many "over-the-counter" medications can have serious effects when used inappropriately for prolonged periods or in conjunction with certain prescriptions. Participants were asked if they tended to consult their physician when using over-the-counter drugs with prescription medicines. The forced choice response options were: never; sometimes; or always. 71% of the participants indicated that they either never (41.3%) or sometimes (29.7%) consulted their doctor when using over-the-counter drugs with prescriptions.

Knowledge of prescription drugs is initially transmitted by a physician or other competent medical authority. Information sources for over-the-counter medications is varied. Efforts were made to identify the sources most commonly used by participants in relation to over-the-counter drugs. Across the three subgroups, physicians were the most popular information source for over-the-counter drugs. Similarly, most relied heavily on advice from the pharmacist as well as mass media advertising. It is curious that among all subgroups, the information on the labels of the medication consistently ranked very low as an information source.

Figure 5

OVER-THE-COUNTER MEDICATION INFORMATION SOURCES

RANKED BY PREFERENCE OF USE

CONGREGATE		DAY CARE		AT LARGE		OVERALL	
Source	%	Source	%	Source	%	Source	%
Doctors	34	Doctors	45.2	Doctors	32.9	Doctors	35.4
Advertising	22.9	Pharmacists	19.1	Pharmacists	26.8	Pharmacists	20.5
Pharmacist	17.4	Advertising	11.9	Advertising	13.4	Advertising	18.3
Friends	13.2	Friends	9.5	Friends	9.8	Friends	11.6
Labels	10.4	Relatives	9.5	Relatives	8.6	Labels	9
Relatives	2.1	Labels	4.8	Labels	8.5	Relatives	5.2

In relation to over-the-counter medication labeling, participants were asked if they were able to read the labels or instructions. The forced choice responses were: never (able to read); sometimes (able to read); or always (able to read). 26.2% of all respondents cited difficulty in reading labels. This could account for the low ranking of labels as an information source for medication.

Figure 6

ABILITY TO READ MEDICINE LABELS

	#	%
ALWAYS	223	73.8%
SOMETIMES	56	18.1%
NEVER	25	8.1%

Experience some difficulty with product labels.

Participants were surveyed regarding their personal use of over-the-counter medications. Eleven common over-the-counter drug types were listed along with the possibility of citing "others". Participants were asked to think of their medicine cabinet and indicate how many of these medications they have at their disposal.

Information regarding the most frequently used over-the counter drugs was provided by respondents. The most popular non-prescription drug used by the elderly is aspirin/pain reliever. The second most frequently used medications over all subgroups were laxatives/diuretics. Overall, the five over-the-counter drug types listed account for approximately 76.1% of the entire over-the-counter drug use of local elderly.

Figure 7

OVER-THE-COUNTER MEDICATIONS
MOST FREQUENTLY UTILIZED MEDICATIONS

CONGREGATE		DAY CARE		AT LARGE		TOTAL	
Medications	%	Medications	%	Medications	%	Medications	%
Aspirin/ Bufferin	24.5	Aspirin/ Bufferin	29.4	Aspirin/ Bufferin	27.2	Aspirin/ Bufferin	25.9
Laxatives/ Diuretics	17.0	Laxatives/ Diuretics	18.5	Vitamins	16.8	Laxatives/ Diuretics	16.3
Vitamins	15.2	Vitamins	14.4	Laxatives/ Diuretics	14.1	Vitamins	15.6
Antacids	9.4	Cough Med.	11.6	Antacids	10.1	Antacids	9.5
Cough Med.	8.4	Antacids	8.2	Cough Med.	8.4	Cough Med.	8.8

These over-the-counter drugs ordinarily harmless to the general population can be a potential danger to the elderly. The drugs listed above are especially hazardous. The prolonged or continual use of aspirin can cause anemia as well as irritate the stomach lining. Abuse of laxatives or diuretics can lead to a functional dependency along with potential dehydration or mineral deficiencies. Use of antacids in conjunction with cardiac medication inhibits effectiveness of both medications. The remedy or preventative most elderly believe to be harmless is vitamins. However, over use or inappropriate use can lead to adverse reactions. In general, it is important to note that most Pinellas elderly have direct access to medications that can cause symptoms simulating those of other diseases of the elderly. The real danger arises when these symptoms are treated as unrelated to the over-the-counter medications is use.

18.9% of the participants indicated no over-the-counter drugs currently on hand. An additional 39.5% had between 1 to 3 different medications on hand. 41.6% of those surveyed possessed 4 or more different over-the-counter medications. "Risk" has been operationally defined as possessing 4 or more different over-the-counter drugs concurrently. Keep in mind that along with the 41.6% of the elderly who have 4 or more over-the-counter drugs on hand 19.4% revealed that they also have 4 or more different prescription medications.

FIGURE 8

QUANTITY OF OVER-THE-COUNTER DRUGS ON HAND

	#	%	
NONE	67	18.9	
1-3	140	39.5	
4-7	128	36.2	[illegible] AT RISK
8-12	19	5.4	
TOTAL	354	100.0%	

Prescription medicine in combination with over-the-counter drugs can yield dangerous results. Previous information indicates that the elderly engage in a variety of self-medicating behaviors. The risk of experiencing problems with over-the-counter medication taken in combination with prescription drugs increases as the frequency of each variable increases.

It is important to review the summary data for the variables of "number of prescriptions on hand at home" and the "number of different over-the-counter drugs on hand at home" individually. However, cross-classification of the two variables provides a more in depth view of the potential risk the elderly face daily in their medicine cabinet.

The quantity of prescription medicine on hand was ploted in relation to the number of different over-the-counter drugs readily available to each respondent. It should be noted that these variables ask for current information regarding the availability of medicine.

Risk levels were established based upon the assumption that the risk of mismedication or incompatiable combinations increases in relation to the quantity of prescribed and over-the counter medicines available.

Level	Definition
"no risk"	"0" prescriptions and "0" over-the-counter drugs on hand
"low risk"	"0" prescriptions on hand and "1-3" over-the-counter drugs on hand or "1-2" prescriptions on hand and "0-3" over-the-counter drugs on hand

Level	Definition
"moderate risk"	"3-6" prescriptions on hand "4-6" over-the-counter drugs on hand
"high risk"	"7" or more prescriptions on hand and "7" or more over-the counter drugs on hand

Data was reviewed on the congregate and day care respondents as a group and the "at large" subgroup separately. Based upon the information available, the at large group subgroup demonstrated significantly higher risk than the congregate/day care group. 70.6% of the at large subgroup cited a risk level of moderate to high. In comparison, the day care/congregate subgroup identified 54.03% in the moderate to high range. Overall, 58.2% of the respondents indicated a risk level from moderate to high. Cross-classification information is available in Figures 9 and 10.

Figure 9

Cross Classification
Quantity of Prescription Drugs on Hand
by
Quantity of Over-The-Counter Drugs on Hand

Congregate and Day Care Subgroups

# Of Different Prescriptions on Hand	# Of Over-The-Counter Drugs On Hand													
	0	1	2	3	4	5	6	7	8	9	10	11	12	Total
NONE	13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	59
1-2 Prescriptions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	135
3-4 Prescriptions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	48
5-6 Prescriptions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	13
7-9 Prescriptions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	5
10 or More	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	9
Total	62	33	39	34	42	23	19	6	6	2	1		2	269

No Risk:	4.8%
Low Risk:	40.9%
Moderate Risk:	42.8%
High Risk:	11.5%

Figure 10

Cross Classification
Quantity of Prescription Drugs on Hand
by
Quantity of Over-The Counter Drugs on Hand
At Large Subgroup

# Of Different Prescriptions on Hand	# Of Over-The-Counter Drugs On Hand: 0	1	2	3	4	5	6	7	8	9	10	11	12	Total
NONE	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	11
1-2 Prescriptions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	41
3-4 Prescriptions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	26
5-6 Prescriptions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4
7-9 Prescriptions	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	3
10 or More	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0
Total	6	7	10	16	11	14	7	6	5	3	0	0	0	85

No Risk:	2.3%
Low Risk:	27.1%
Moderate Risk:	50.6%
High Risk:	20.0%

From the information provided it appears as though Pinellas County elderly have access to considerable amounts of prescriptions as well as over-the-counter drugs; that they engage in self-diagnostic and medication behaviors with a moderate amount of knowledge of the potential side effects of the medications used. This information suggests that the elderly are at some risk of medication misuse.

IV. Unsafe Medication Behaviors

Several factors explored in the survey can be considered unsafe medication practices. The following behaviors are considered unsafe:

*discontinuance of medication if feeling better
*saving old/leftover medication for future use

*phoning the doctor for a prescription instead of a visit
*when sick engaging in a self diagnostic/medication practice
  - buying something from the store
  - use of an old prescription
  - borrowing medicine from a friend
  - use of a home remedy

*using over-the-counter and prescribed medicines concurrently with little or no consultation with the doctor
*missed taking prescriptions

**this behavior is not assessed in the short survey administered at the "Senior Citizens Showcase of Services".

Information was available on the prevalence of each unsafe medication behavior. Figure 11 provides a rank order review of the percentage involvement of participants with the various unsafe practices. The most frequently cited unsafe practice was the concurrent use of over-the-counter drugs and prescription medication with little or no consultation with the physician. Self diagnosis/medication ranked second for the congregate and day care groups. The behavior ranked second for the at large group was missing a prescription. Of the unsafe medicating behaviors, the least frequently cited was discontinued use if the participant perceived relief.

Figure 11

Unsafe Medication Practices	Congregate	Day Care	At Large	Overall
using over the counter and prescription drugs without consulting a doctor	69.4%	71.4%	74.6%	70.0%
self diagnosis/ medicating	77.6%	69.2%	N/A	57.5%
phoned doctor for prescription	41.9%	35.6%	50.6%	42.9%
missed prescription	40.0%	17.5%	65.2%	41.6%
failed to discard old medications	38.9%	32.3%	33.3%	36.3%
discontinued prescription if feeling better	22.4%	12.0%	25.4%	21.3%

Previously each behavior was reviewed independently. However, the potential deleterious impact is compounded when participants responses are reviewed to identify their total involvement in unsafe behaviors. Information regarding unsafe practices was available on all subgroups. The "at large" group was not questioned about self-diagnostic/medicating behaviors. Therefore, the at large group had a maximum score of 5 for unsafe behaviors as oppossed to a maximum score of 6 for the congregate and day care groups.

Results indicate that overall 83.1% of the participants identified involvement in at least one unsafe medication practice. Additionally, it is of value to review the extent of respondent's involvement with unsafe medication practices. An index of unsafe medication behaviors ranged from no involvement to involvement in all 6 (5 for at large respondents) behaviors. Operational definitions include: 1)low involvement with only one unsafe behavior; 2)moderate involvement with 2-4 unsafe behaviors; and 3) high involvement with 5-6 unsafe behaviors. It is important to realize that the moderate range by no means implies "normal" behavior. The moderate category accounts for 33% to 67% involvement with the unsafe behaviors cited. Figure 12 displays the unsafe medication practice multiple involvement index. The highest concentration of responses was in the moderate range. It is interesting to note that almost 10% of the congregate respondents exhibited a high level of involvement in unsafe medication practices.

Figure 12

Rate of Involvement in Unsafe Medication Practices

All Groups

Level of Involvement		Congregate		Day Care		At Large		Total		
		#	%	#	%	#	%	#	%	
No	0	34	16.6	11	17.0	15	17.6	60	16.9	
Low	1	52	25.4	24	36.9	19	22.4	95	26.8	83.1%
Moderate	2-4	99	48.3	28	43.1	48	56.5	175	49.3	
High	5-6	20	9.7	2	1.0	3	3.5	25	7.0	
	Total	205	100.0	65	100.0	85	100.0	355	100.0	

V. "At Risk" Indicators

Available research continually cites the disproportionate involvement of the elderly in the use of medication. Additional information is available upon the variables and extent of such use. A concern among elderly service providers is how summary information on elderly drug use can be translated into an at risk indicator for the target population.

Throughout the survey, participants were asked questions whose subject matter dealt primarily with risk. There are 11 such questions in the general survey and 9 in the abbreviated version completed at the Senior Showcase of Services. An "at risk" index can be established using these factors. The variables that comprise the risk index are as follows:

Variable	Question # Corresponding to Variable	
	Long	Short
Living alone	2	2
Taking 2 or more prescriptions	6	5
Medicating more than Once a day	14	7
More than 2 prescriptions at home	17	N/A
Unaware of side effects	19	6
Missed medication due to forgetfulness	25	9
Missed medication but remedicated upon discovery	26	10
More than 3 over-the-counter drugs at home	31	20
Medicines similar in shape or color	29	19
Unable to read labels	34	17
Unable to distinguish between medicines	35	N/A
Maximum Risk Score	11	9

The various "at risk" factors have been grouped into four levels. The limits of the risk levels are as follows:

Low Risk	1-2 risk factors
Moderate Risk	3-5 risk factors
High Risk	6-9 risk factors
Extremely High Risk	10-12 risk factors*

*not available on "at large" respondents

Figure 14

"At Risk" Levels

Level of Involvement	Congregate		Day Care		At Large		Total	
	#	%	#	%	#	%	#	%
No Risk	5	2.4	6	9.2	3	3.5	14	3.9
Low Risk	81	39.5	18	27.7	41	48.2	140	39.4
Moderate Risk	95	46.4	34	52.3	38	44.8	167	47.0
High Risk	23	11.2	7	10.8	3	3.5	33	9.3
Extremely High Risk	1	.5	0	0	N/A	N/A	1	.3

Overall, 96.1% of the respondents cited at least one "at risk" factor. Approximately, 47% of all participants cited a risk level in the moderate range. For program development purposes, those citing low risk values, 39.4% overall, are an appropriate target group for education and prevention strategies. The moderate through extremely high range present an opportunity for intervention and education efforts. Since over 56% of the respondents cited risk levels of moderate and beyond, there appears to be a significant population that would benefit from elder ed services.

VI. Discussion

Question by question comparison of results of the initial elder-med survey and the present instrument are not possible. Questions were reworded for greater clarity. However, there are questions that are comparable. The initial survey cited 76% prescription use as compared to 68.4% in the current sample. This difference is reflective of the current study group exhibiting 49.1% involvement with over-the-counter medications.

The reliance and prevalence of over-the-counter drugs in the 1983 group is highlighted when reviewing unsafe medication practices. The major unsafe medication practice reported by respondents in the initial survey was to skip prescribed medications. Although this behavior may interrupt treatment and forestall recovery, it is not as potentially dangerous as the practice of taking prescribed medications along with over-the-counter drugs without the doctor's knowledge. The latter was cited in the 1983 study as the most prevalent unsafe practice. This practice could lead to the consumption of medications that could be contraindicated and produce serious side effects.

The results of the 1983 elder-med survey indicate the following:

1. A large percentage (68.4%) of the elderly resident population are consumers of prescription medicine.

2. Pinellas County elderly are not only consumers of prescription medicine, but almost half (49.1%) of the population indicate use of over-the-counter medicines.

3. 44.5% of the elderly population frequently use over-the-counter medication in conjunction with prescribed medicines with little or no consultation with their doctor.

4. Approximately 83.1% of the elderly population engage in at least one unsafe medication practice.

5. Over half (56.3%) of the population indicated moderate to high levels of involvement in unsafe medication practices.

6. The risk of a medication error is increased in relation to the total number of risk factors that can be ascribed to a respondent. Almost 10% of the survey respondents' risk scores fell in the high range. An additional 47% cited a moderate risk level.

7. Finally the data suggest that the majority of the elderly engage in unsafe medication behaviors and are "at risk" of medication mismanagement.

VII. Summary/Conclusion

Given the involvement of youth in drug use and misuse throughout the United States, it is not surprising that research and program development are geared toward a younger target population. Available data suggest that the elderly while disproportionately consume prescription and over-the-counter drugs in relation to their representation in the general population, are at a higher risk of potential misuse of these substances. Operation PAR, Inc. is committed to prevention, education and intervention strategies for drug and substance abuse for all age levels.

The objective of the elder-med study was to identify and synthesize information on the use and misuse of prescription and over-the-counter drugs among the elderly. Study results indicate that a concern for the high rate of medication use and mismanagement among the elderly is warranted. Underreporting is common to all age groups on sensitive subjects and is an expected reaction in self-report inquiries. Thus, the true dimensions of the drug use/misuse practices of the Pinellas County elderly may only be estimated from the data.

However, the elder-med survey results serve to reinforce the need for medication management services for the elderly. Education and prevention efforts should be concentrated on the dynamics of medication use/misuse in relation to the aging process. Another area for service development would be to make the general population sensitive to the potential dangers of dealing with the aged through medication. Pinellas County elderly are "at risk" with respect to medication use/misuse, although the risk can be managed through the delivery of elder-med services.

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
Sources of Information on Over-The-Counter Medicine:								
Advertising	33	22.9	5	11.9	11	13.4	49	18.3
Friends	19	13.2	4	9.5	8	9.8	31	11.6
Relatives	3	2.1	4	9.5	7	8.6	14	5.2
Pharmacists	25	17.4	8	19.1	22	26.8	55	20.5
Labels	15	10.4	2	4.8	7	8.5	24	9.0
Doctors	49	34.0	19	45.2	27	32.9	95	35.4
Total	144	100%	42	100%	82	100%	268	100%
Over-The-Counter Medicine Currently on Hand at Home								
Aspirin/Buferin	151	24.5	43	29.4	94	27.2	288	25.9
Antacids	58	9.4	12	8.2	35	10.1	105	9.5
Laxatives/Diuretics	105	17.0	27	18.5	49	14.1	181	16.3
Iron Pills	26	4.2	3	2.1	10	2.9	39	3.5
Mineral Oil	15	2.4	3	2.1	3	.9	21	1.9
Cold Medicine	49	7.9	9	6.2	23	6.6	81	7.3
Cough Medicine	52	8.4	17	11.6	29	8.4	98	8.8
Nasal Spray	20	3.2	7	4.8	21	6.1	48	4.3
Sleeping Pills	20	3.2	4	2.7	11	3.2	35	3.2
Vitamins	94	15.2	21	14.4	58	16.8	173	15.6
Other	28	4.6			13	3.7	41	3.7
Total	618	4.6	146	100%	346	100%	1,110	100%

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
Number Of Different Over-The-Counter Medicine On Hand At Home:	#	%	#	%	#	%	#	%
NONE	42	20.5	20	31.3	5	5.9	67	18.9
1	23	11.2	10	15.6	8	9.4	41	11.6
2	32	15.6	7	10.9	10	11.8	49	13.8
3	23	11.2	11	17.2	16	18.8	50	14.1
4	35	17.1	7	10.9	11	12.9	53	15.0
5	19	9.3	4	6.3	14	16.5	37	10.5
6	14	6.8	5	7.8	7	8.2	26	7.3
7	6	2.9	---	----	6	7.1	12	3.4
8	6	2.9	---	----	5	5.9	11	3.1
9	2	1	---	----	3	3.5	5	1.4
10	1	.5	---	----	---	---	1	.3
11	--	---	---	----	---	---	---	---
12	2	1	---	----	---	---	2	.6
TOTAL	205	100	64	100	85	100	354	
Experienced Trouble With Packaging Of Medicine:								
YES	58	36.3	12	24.	42	52.5	112	38.6
NO	102	63.7	38	76.	38	47.5	178	61.4
TOTAL	160		50		80		290	100

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
Medicine Is Kept:	#	%	#	%	#	%	#	%
Bathroom	93	49.5	22	35.5	---	---	115	46
Kitchen	53	28.2	21	33.9	---	---	74	29.6
Bedroom	29	15.4	15	24.2	---	---	44	17.6
Other	13	6.9	4	6.4	---	---	17	6.8
TOTAL	188		62		----	---	250	
Are Any Medicines Similar in Color/ Shape:								
YES	23	18.7	15	29.4	18	27.7	56	23.4
NO	100	81.3	36	70.6	47	72.3	183	76.6
TOTAL	123		51		65	100	239	100
Able To Read Labels/ Instructions:								
Never	15	8.3	8	14.6	2	2.8	25	8.1
Sometimes	27	14.9	13	23.6	16	21.9	56	18.1
Always	139	76.8	34	61.8	55	75.3	228	73.8
TOTAL	181		55		73		309	
Difficult to Distinguish One Medicine From Another:								
Never	111	68.9	34	59.7	---	----	145	66.5
Sometimes	37	23	15	26.3	---	----	52	23.9
Always	13	8.1	8	14.0	---	----	21	9.6
TOTAL	161		57	100	---	----	218	

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
Sex:								
Male	102	49.5	16	24.6	24	28.2	142	39.9
Female	104	50.5	49	75.4	61	71.8	214	60.1
Total	206	100%	65	100%	85	100%	356	100%
Living Arrangements:								
Alone	116	56.6	25	38.5	28	34.6	169	48.1
w/spouse	59	28.9	8	12.3	52	64.2	119	33.9
w/family	20	9.7	25	38.5	1	1.2	46	13.1
w/friends	7	3.4	3	4.6			10	2.9
Group Care	3	1.4	4	6.1			7	2.0
Total	205	100%	65	100%	81	100%	351	100%
Age:								
60-69	60	30.0	15	23.8	44	53.0	119	34.4
70-79	85	42.5	19	30.2	32	38.6	136	39.3
80 and over	55	27.5	29	46.0	7	8.4	91	26.3
Total	200	100%	63	100%	83	100%	346	100%
Financial:								
Social Sec.	190	70.6	55	69.6	70	72.2	315	70.9
Pension	60	22.3	6	7.6	27	27.8	93	20.9
Food Stamps	10	3.7	7	8.9			17	3.8
Welfare	4	1.5	6	7.6			10	2.2
Other Assist.	5	1.9	5	6.3			10	2.2
Total	269	100%	79	100%	97	100%	445	100%
Multiple Financial Sources	55		16		21		92	

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
Under Doctor's Care:								
Yes	129	63.8	48	76.2	-	-	177	66.8
No	73	36.2	15	23.8	-	-	88	32.2
Total	202	100%	63	100%			265	100%
Suffer From:								
Colds	73	14.1	26	15.0			99	14.7
Flu	28	5.4	10	5.8			38	5.7
Headaches	36	6.9	12	6.9			48	7.1
Coughs	39	7.5	12	6.9			51	7.6
Stomach Prob.	31	6.0	8	4.6			39	5.8
Arthritis	89	17.2	28	16.2			117	17.4
High Blood Pressure	68	13.1	23	13.3			91	13.6
Gas/Indigestion	44	12.3	17	9.9			61	9.1
Leg Cramps	69	13.3	28	16.2			97	14.4
Chest Pain	22	4.2	9	5.2			31	4.6
Total	499	100%	173	100%			672	100%
Multiple Complaints:								
1	37	17.9	8	12.3			45	16.6
2	32	15.5	10	15.4			42	15.5
3	27	13.1	10	15.4			37	13.6
4	17	8.2	9	13.9			26	9.6
5	14	6.8	4	6.2			18	6.6
6	9	4.4	4	6.2			13	4.8
7	7	3.4	2	3.0			9	3.3
8	3	1.5	2	3.0			5	1.9
9	3	1.5	1	1.5			4	1.5
10	1	.5					1	.4
0	56	27.2	15	23.1			71	26.2
Total	206	100%	65	100%			271	100%

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
Description of General Health:								
Poor	9	4.3	5	7.9			14	5.2
Fair	74	35.8	25	39.7			99	36.6
Good	104	50.2	28	44.5			132	48.9
Excellent	20	9.7	5	7.9			25	9.3
Total	207	100%	63	100%			270	100%
Frequency of Doctor's Visit:								
Once a month	36	19.3	16	25.9			52	21.0
Twice a year	71	38.2	11	17.7			82	33.0
Once a year	40	21.5	11	17.7			51	20.5
Other	39	21.0	24	38.7			63	25.4
Total	186	100%	62	100%			248	100%
Sick Days in Past 2 Months:								
#Days	552		109				661	
#Respondents	158		34				192	
Average	3.5		3.2				3.4	
Taking Prescribed Medicine:								
Yes	129	65.5	46	78.0			175	68.4
No	68	34.5	13	22.0			81	31.6
Total	197	100%	59	100%			256	100%

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
Number of Prescribed Medicines Being Taken:								
1-2	113	69.3	22	46.8	41	55.4	176	62.0
3-4	27	16.6	21	44.7	26	35.1	74	26.0
5-6	9	5.5	4	8.5	4	5.4	17	6.0
7-9	5	3.1			3	4.1	8	2.8
10 or more	9	5.5					9	3.2
Total	163	100%	47	100%	74	100%	284	100%
Times Medicated Daily:								
1	62	41.3	15	27.8	21	34.4	98	37.7
2	40	26.7	15	27.8	12	19.7	67	25.8
3	26	17.3	16	29.6	15	24.6	57	21.9
4	17	11.3	3	5.5	12	19.7	32	12.3
More	5	3.4			1	1.6	6	2.3
Total	150	100%	49	100%	61	100%	260	100%
Quite Taking Medicine if Feeling Better:								
Yes	39	22.4	6	12	16	25.4	61	21.3
No	135	77.6	44	88	47	74.6	226	78.7
Total	174	100%	50	100%	63	100%	287	100%

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
Disposition of Leftover Medicine:								
Save for Later	52	36.1	13	28.3	23	33.3	88	34.0
Throw Out	88	61.1	31	67.4	46	66.7	165	63.7
Share	4	2.8	2	4.3			6	2.3
Total	134	100%	46	100%	69	100%	259	100%
Number of Different Prescriptions on Hand Today:								
1-3	123	69.9	38	67.8			161	69.4
4-6	24	13.6	8	14.3			32	13.8
7-9	8	4.6	2	3.6			10	4.3
10 or more	3	1.7					3	1.3
0	18	10.2	8	14.3			26	11.2
Total	176	100%	56	100%			232	100%
Phoned Doctor For Prescription:								
Yes	77	41.9	21	35.6	40	50.6	138	42.9
No	107	58.1	38	64.4	39	49.4	184	57.1
Total	184	100%	59	100%	79	100%	322	100%
Aware of Medicine Side Effects:								
Yes	109	72.7	26	48.1	49	65.3	184	65.9
No	41	27.3	28	51.9	26	34.7	95	34.1
Total	150	100%	54	100%	75	100%	279	100%

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
When Sick and Did Not Go to the Doctor, I:								
Buy Something from Store	32	20.1	7	15.6			39	19.1
Use Old Prescription	17	10.7	7	15.6			24	11.8
Borrow from Friends	1	.6					1	.5
Use Home Remedy	29	18.3	2	4.4			31	15.2
Talk to Pharmacist	17	10.7	2	4.4			19	9.3
Phone Doctor for Prescription	17	10.7	5	11.1			22	10.8
Nothing	46	28.9	22	48.9			68	33.3
Total	159	100%	45	100%			204	100%
Use Over The Counter Medicine:								
Yes	84	48	27	52.9			111	49.1
No	91	52	24	47.1			115	50.9
Total	175	100%	51	100%			226	100%
Use Over The Counter w/Prescriptions:								
Yes	81	44.3	25	45.5	35	44.3	141	44.5
No	102	55.7	30	54.5	44	55.7	176	55.5
Total	183	100%	55	100%	79	100%	317	100%

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
Consult Doctor When Using Over-The-Counter Medication:								
Never	61	41.5	21	42.8	25	39.7	107	41.3
Sometimes	41	27.9	14	28.6	22	34.9	77	29.7
Always	45	30.6	14	28.6	16	25.4	75	29
Total	147	100%	49	100%	63	100%	259	100%
Missed Taking Prescription:								
Yes	64	40	10	17.5	45	65.2	119	41.6
No	96	60	47	82.5	24	34.8	167	58.4
Total	160	100%	57	100%	69	100%	286	100%
Reasons for Missing Prescription:								
Felt Better	18	17.3	6	28.6	3	5.9	27	15.3
Forgot	66	63.5	12	57.1	40	78.4	118	67.1
Felt Worse	3	2.9	2	9.5	3	5.9	8	4.6
Did Not Help	9	8.6	1	4.8	2	3.9	12	6.8
Other	8	7.7			3	5.9	11	6.2
Total	104	100%	21	100%	51	100%	176	100%
Response to Missed Prescription:								
Take another pill	11	12.8	3	14.3	6	13.7	20	13.2
Wait Until Next Time	68	79.1	17	80.9	28	63.6	113	74.8
Other	7	8.1	1	4.8	10	22.7	18	12
Total	86	100%	21	100%	44	100%	151	100%

	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
Cost Of Medicine A Hardship:	#	%	#	%	#	%	#	%
YES	66	41.5	21	36.8	---	----	87	40.3
NO	93	58.5	36	63.2	---	----	129	59.7
TOTAL	159	100	57	100	---	----	217	100
Monthly Medical Expense:								
Dollars	3124		570		---		3694	
N	119		28		---		147	
Average	$26.25		$20.36		---		$25.13	
Unsafe Medication Practices								
1	52	25.4	24	36.9	19	22.4	95	26.8
2	44	21.5	15	23.1	18	21.2	77	21.7
3	34	16.6	10	15.4	19	22.4	63	17.8
4	21	10.2	3	4.6	11	12.9	35	9.8
5	12	5.8	1	1.5	3	3.5	16	4.5
6	8	3.9	1	1.5	N/A	N/A	9	2.5
0	34	16.6	11	17.0	15	17.6	60	16.9
TOTAL	205	100	65	100	85	100	355	100

Number Of Risk Factors Indicated	CONGREGATE		DAY CARE		AT LARGE		TOTAL	
	#	%	#	%	#	%	#	%
1	33	16.1	5	7.7	16	18.8	54	15.2
2	48	23.4	13	20	25	29.4	86	24.2
3	49	23.9	10	15.4	20	23.5	79	22.3
4	27	13.2	14	21.5	11	12.9	52	14.7
5	19	9.3	10	15.4	7	8.2	36	10.1
6	13	6.3	3	4.6	3	3.6	19	5.4
7	8	3.9	2	3.1	--	----	10	2.8
8	2	1	2	3.1	--	----	4	1.1
9	--	----	--	---	--	----	--	----
10	1	.5	--	---	--	----	1	.3
11	--	----	--	---	--	----	--	----
12	--	----	--	---	--	----	--	----
0	5	2.4	6	9.2	3	3.6	14	3.9
TOTAL	205	100	65	100	85	100	355	100

APPENDIX B

Completion Percentages For Survey Questions

Question	N	Number Of Responses	%	Question	N	Number Of Responses	%
1	356	356	100	19	271	204	75.3
2	356	351	98.6	20	271	226	83.4
3	356	346	97.2	21	356	317	89.0
4	356	353	95.1	22	356	259	72.8
5	356	265	74.4	23	356	286	80.3
6	356	271	76.1	24	---	---	----
7	271	271	100	25	---	---	----
8	271	270	99.6	26	356	268	75.3
9	271	248	91.5	27	---	---	----
10	---	---	----	28	---	---	----
11	271	256	94.5	29	356	290	81.5
12	356	284	79.8	30	271	250	92.3
13	356	260	73	31	356	239	67.1
14	356	287	80.6	32	356	309	86.8
15	356	259	72.8	33	271	218	80.4
16	271	232	85.6	34	271	216	79.7
17	356	322	90.4	35	---	---	----
18	356	279	78.4	--	---	---	----

APPENDIX 2

504

CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION
CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

PPA CONTAINING DRUGS

	AGE	COSTART	TOTAL OCCURRENCES
BODY AS A WHOLE			
COSTART	COUNT	ADRENERG SYND	1
COSTART	COUNT	ALLERG REACT	2
COSTART	COUNT	ANAPHYL	4
COSTART	COUNT	ANOMALY CONGEN	5
COSTART	COUNT	ANTICHOLINERG SYND	1
COSTART	COUNT	ASTHENIA	4
COSTART	COUNT	CHILLS	1
COSTART	COUNT	CHILLS FEVER	1
COSTART	COUNT	DEATH	1
COSTART	COUNT	EDEMA FACE	4
COSTART	COUNT	FEVER	2
COSTART	COUNT	HEADACHE	7
COSTART	COUNT	INFECT	1
COSTART	COUNT	MALAISE	1
COSTART	COUNT	OVERDOSE	1
COSTART	COUNT	OVERDOSE ACCID	3
COSTART	COUNT	OVERDOSE INTENT	1
COSTART	COUNT	PAIN	1
COSTART	COUNT	PAIN ABDO	2
COSTART	COUNT	PAIN CHEST	3
COSTART	COUNT	SERUM SICK	1
COSTART	COUNT	SHOCK	1

```
  FPA CONTAINING DRUGS

-------------------------------------------------------------------------------------------------------------
                  AGE          COSTART             TOTAL
                                                OCCURRENCES
-------------------------------------------------------------------------------------------------------------

  BODY AS A WHOLE

AGE      COUNT                                       48
COSTART  COUNT    0  HEADACHE                         1
COSTART  COUNT    0  NO DRUG EFFECT                   1
COSTART  COUNT    0  OVERDOSE                         1
AGE      COUNT    0                                   3
COSTART  COUNT    1  ANOMALY CONGEN MULT              1
COSTART  COUNT    1  DEATH                            1
COSTART  COUNT    1  ECTROMELIA                       1
COSTART  COUNT    1  OVERDOSE ACCID                   1
COSTART  COUNT    1  SERUM SICK                       1
AGE      COUNT    1                                   5
COSTART  COUNT    2  ALLERG REACT                     1
COSTART  COUNT    2  OVERDOSE ACCID                   1
AGE      COUNT    2                                   2
COSTART  COUNT    3  OVERDOSE ACCID                   2
AGE      COUNT    3                                   2
COSTART  COUNT    4  OVERDOSE ACCID                   1
AGE      COUNT    4                                   1
COSTART  COUNT    7  ASTHENIA                         1
AGE      COUNT    7                                   1
COSTART  COUNT    8  ASTHENIA                         1
```

260

```
 PPA CONTAINING DRUGS

-----------------------------------------------------------------------------------------
                  AGE        COSTART          TOTAL
                                           OCCURRENCES
-----------------------------------------------------------------------------------------

 BODY AS A WHOLE

AGE      COUNT    8                               1
COSTART  COUNT   11  ALLERG REACT                 1
AGE      COUNT   11                               1
COSTART  COUNT   15  EDEMA FACE                   1
AGE      COUNT   15                               1
COSTART  COUNT   17  ANAPHYL                      1
COSTART  COUNT   17  FEVER                        1
AGE      COUNT   17                               2
COSTART  COUNT   18  OVERDOSE INTENT              2
AGE      COUNT   18                               2
COSTART  COUNT   19  OVERDOSE INTENT              1
AGE      COUNT   19                               1
COSTART  COUNT   20  HEADACHE                     1
COSTART  COUNT   20  OVERDOSE INTENT              2
COSTART  COUNT   20  PAIN                         1
AGE      COUNT   20                               4
COSTART  COUNT   22  HEADACHE                     1
AGE      COUNT   22                               1
COSTART  COUNT   23  OVERDOSE INTENT              1
AGE      COUNT   23                               1
COSTART  COUNT   24  ECTROMELIA                   1
COSTART  COUNT   24  OVERDOSE                     1
```

```
 PPA CONTAINING DRUGS
------------------------------------------------------------------------------------------------
                    AGE          COSTART          TOTAL
                                               OCCURRENCES
------------------------------------------------------------------------------------------------
 BODY AS A WHOLE

AGE      COUNT   24                                 2
COSTART  COUNT   26  HEADACHE                       2
AGE      COUNT   26                                 2
COSTART  COUNT   27  ANTICHOLINERG SYND             1
COSTART  COUNT   27  HEADACHE                       4
COSTART  COUNT   27  PAIN CHEST                     1
AGE      COUNT   27                                 6
COSTART  COUNT   28  ANAPHYL                        1
COSTART  COUNT   28  EDEMA FACE                     2
COSTART  COUNT   28  HEADACHE                       1
AGE      COUNT   28                                 4
COSTART  COUNT   30  ALLERG REACT                   1
COSTART  COUNT   30  HEADACHE                       1
AGE      COUNT   30                                 2
COSTART  COUNT   31  EDEMA FACE                     1
COSTART  COUNT   31  INFECT                         1
AGE      COUNT   31                                 2
COSTART  COUNT   32  ANOMALY CONGEN                 1
COSTART  COUNT   32  HEADACHE                       1
COSTART  COUNT   32  SERUM SICK                     1
AGE      COUNT   32                                 3
```

```
  PPA CONTAINING DRUGS

-----------------------------------------------------------------------------------------------------------------------------------
                AGE          COSTART          TOTAL
                                            OCCURRENCES
-----------------------------------------------------------------------------------------------------------------------------------

  BODY AS A WHOLE
COSTART  COUNT   33  ANAPHYL                   1
COSTART  COUNT   33  ECTROMELIA                1
COSTART  COUNT   33  EDEMA FACE                1
COSTART  COUNT   33  HEADACHE                  1
AGE      COUNT   33                            4
COSTART  COUNT   34  ANAPHYL                   1
COSTART  COUNT   34  EDEMA FACE                1
COSTART  COUNT   34  HEADACHE                  1
AGE      COUNT   34                            3
COSTART  COUNT   35  ANAPHYL                   2
AGE      COUNT   35                            2
COSTART  COUNT   36  PAIN CHEST                1
AGE      COUNT   36                            1
COSTART  COUNT   37  SERUM SICK                1
AGE      COUNT   37                            1
COSTART  COUNT   38  PAIN CHEST                1
COSTART  COUNT   38  WITHDRAW SYND             1
AGE      COUNT   38                            2
COSTART  COUNT   43  EDEMA FACE                1
AGE      COUNT   43                            1
COSTART  COUNT   45  HEADACHE                  1
AGE      COUNT   45                            1
```

```
06/21/83                    CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION                 PAGE 64
                              CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES
 PPA CONTAINING DRUGS
--------------------------------------------------------------------------------------------------------
                 AGE          COSTART             TOTAL
                                               OCCURRENCES
--------------------------------------------------------------------------------------------------------
 BODY AS A WHOLE

COSTART  COUNT   46  ASTHENIA                      1
AGE      COUNT   46                                1
COSTART  COUNT   48  HEADACHE                      1
COSTART  COUNT   48  PAIN                          1
AGE      COUNT   48                                2
COSTART  COUNT   49  EDEMA FACE                    1
AGE      COUNT   49                                1
COSTART  COUNT   50  OVERDOSE                      1
AGE      COUNT   50                                1
COSTART  COUNT   51  PAIN ABDO                     1
COSTART  COUNT   51  PAIN CHEST                    1
AGE      COUNT   51                                2
COSTART  COUNT   54  SERUM SICK                    1
AGE      COUNT   54                                1
COSTART  COUNT   55  ASTHENIA                      1
COSTART  COUNT   55  HEADACHE                      1
COSTART  COUNT   55  PAIN CHEST                    1
AGE      COUNT   55                                3
COSTART  COUNT   56  ASTHENIA                      1
COSTART  COUNT   56  CEREBROVASC ACCID             1
COSTART  COUNT   56  NO DRUG EFFECT                1
```

```
 PPA CONTAINING DRUGS

---------------------------------------------------------------------------------------------------
                AGE         COSTART          TOTAL
                                          OCCURRENCES
---------------------------------------------------------------------------------------------------

 BODY AS A WHOLE

AGE      COUNT   56                           3
COSTART  COUNT   58  MALAISE                  1
AGE      COUNT   58                           1
COSTART  COUNT   60  HEADACHE                 1
AGE      COUNT   60                           1
COSTART  COUNT   62  HEADACHE                 1
COSTART  COUNT   62  OVERDOSE                 1
AGE      COUNT   62                           2
COSTART  COUNT   64  HEADACHE                 1
COSTART  COUNT   64  NO DRUG EFFECT           1
COSTART  COUNT   64  PAIN                     1
AGE      COUNT   64                           3
COSTART  COUNT   74  INFECT                   1
AGE      COUNT   74                           1
COSTART  COUNT   85  PAIN ABDO                1
AGE      COUNT   85                           1
COSTART  COUNT   88  HEADACHE                 1
COSTART  COUNT   88  PAIN CHEST               1
AGE      COUNT   88                           2
COSTART  COUNT   95  ALLERG REACT             1
AGE      COUNT   95                           1
BODYCLAS COUNT                              138
```

36 over age 55
22 over age 60
10 over age 65

```
06/21/83                     CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION                 PAGE 66
                               CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES
 PPA CONTAINING DRUGS

----------------------------------------------------------------------------------------------------------------
             AGE          COSTART          TOTAL
                                         OCCURRENCES
----------------------------------------------------------------------------------------------------------------

 BODY AS A WHOLE


 CARDIOVASCULAR SYSTEM
COSTART  COUNT       ANGINA PECTORIS        3
COSTART  COUNT       CEREBROVASC ACCID      2
COSTART  COUNT       HEART ARREST           2
COSTART  COUNT       HYPERTENS              3
COSTART  COUNT       MIGRAINE               2
COSTART  COUNT       PALPITAT               3
COSTART  COUNT       PERICARDITIS           1
COSTART  COUNT       SHOCK                  1
COSTART  COUNT       SYNCOPE                3
COSTART  COUNT       VASCULITIS             1
COSTART  COUNT       VASODILAT              1
AGE      COUNT                             22
COSTART  COUNT    0  THROM CEREBR           1
AGE      COUNT    0                         1
COSTART  COUNT    3  VASCULITIS             1
AGE      COUNT    3                         1
COSTART  COUNT    4  HEART ARREST           1
COSTART  COUNT    4  TACHYCARDIA            1
AGE      COUNT    4                         2
COSTART  COUNT    8  TACHYCARDIA            1
```

PPA CONTAINING DRUGS

		AGE	COSTART	TOTAL OCCURRENCES
CARDIOVASCULAR SYSTEM				
AGE	COUNT	8		1
COSTART	COUNT	12	HYPERTENS	1
COSTART	COUNT	12	TACHYCARDIA	1
AGE	COUNT	12		2
COSTART	COUNT	13	HYPERTENS	1
COSTART	COUNT	13	SYNCOPE	1
AGE	COUNT	13		2
COSTART	COUNT	16	SHOCK	1
AGE	COUNT	16		1
COSTART	COUNT	19	HEART ARREST	1
AGE	COUNT	19		1
COSTART	COUNT	20	HYPERTENS	2
AGE	COUNT	20		2
COSTART	COUNT	21	EXTRASYSTOLES	1
COSTART	COUNT	21	PALPITAT	2
AGE	COUNT	21		3
COSTART	COUNT	22	HYPERTENS	1
AGE	COUNT	22		1
COSTART	COUNT	25	HYPERTENS	1
COSTART	COUNT	25	HYPOTENS	1
COSTART	COUNT	25	PALPITAT	2

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PPA CONTAINING DRUGS

```
-----------------------------------------------------------------------------------------
                AGE         COSTART          TOTAL
                                          OCCURRENCES
-----------------------------------------------------------------------------------------

 CARDIOVASCULAR SYSTEM

COSTART   COUNT   25  TACHYCARDIA                 2
AGE       COUNT   25                              6
COSTART   COUNT   26  HEART ARREST                1
COSTART   COUNT   26  HYPERTENS                   2
AGE       COUNT   26                              3
COSTART   COUNT   27  HYPERTENS                   2
COSTART   COUNT   27  TACHYCARDIA                 1
AGE       COUNT   27                              3
COSTART   COUNT   28  ECG ABNORM                  1
COSTART   COUNT   28  INFARCT MYOCARD             1
COSTART   COUNT   28  SYNCOPE                     1
AGE       COUNT   28                              3
COSTART   COUNT   30  ANOMALY HEART               1
AGE       COUNT   30                              1
COSTART   COUNT   31  HYPERTENS                   1
AGE       COUNT   31                              1
COSTART   COUNT   32  HEM INTRACRAN               1
COSTART   COUNT   32  HYPERTENS                   1
AGE       COUNT   32                              2
COSTART   COUNT   33  HEART ARREST                1
COSTART   COUNT   33  HYPERTENS                   1
AGE       COUNT   33                              2
```

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```
 06/21/83                        CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION                    PAGE 69
                                  CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES
   PPA CONTAINING DRUGS
-----------------------------------------------------------------------------------------------------------------
                    AGE          COSTART          TOTAL
                                               OCCURRENCES
-----------------------------------------------------------------------------------------------------------------
   CARDIOVASCULAR SYSTEM

 COSTART  COUNT   34  HYPERTENS                   1
 AGE      COUNT   34                              1
 COSTART  COUNT   36  MIGRAINE                    1
 AGE      COUNT   36                              1
 COSTART  COUNT   37  PERICARDITIS                1
 AGE      COUNT   37                              1
 COSTART  COUNT   38  VASODILAT                   1
 AGE      COUNT   38                              1
 COSTART  COUNT   40  HEM INTRACRAN               1
 AGE      COUNT   40                              1
 COSTART  COUNT   41  SYNCOPE                     1
 AGE      COUNT   41                              1
 COSTART  COUNT   43  HYPOTENS POST               1
 AGE      COUNT   43                              1
 COSTART  COUNT   44  HYPERTENS                   1
 AGE      COUNT   44                              1
 COSTART  COUNT   46  PALPITAT                    1
 COSTART  COUNT   46  TACHYCARDIA                 1
 AGE      COUNT   46                              2
 COSTART  COUNT   47  HEM INTRACRAN               1
 COSTART  COUNT   47  HYPERTENS                   1
```

PPA CONTAINING DRUGS

```
------------------------------------------------------------------------------------------------
                 AGE         COSTART          TOTAL
                                           OCCURRENCES
------------------------------------------------------------------------------------------------

CARDIOVASCULAR SYSTEM
AGE       COUNT   47                            2
COSTART   COUNT   48  BRADYCARDIA               1
AGE       COUNT   48                            1
COSTART   COUNT   51  BRADYCARDIA               1
COSTART   COUNT   51  ENCEPHALOP HYPERTENS      1
COSTART   COUNT   51  HYPOTENS                  1
AGE       COUNT   51                            3
COSTART   COUNT   53  HYPOTENS                  1
COSTART   COUNT   53  SYNCOPE                   1
AGE       COUNT   53                            2
COSTART   COUNT   55  CEREBROVASC ACCID         1
COSTART   COUNT   55  SYNCOPE                   1
AGE       COUNT   55                            2
COSTART   COUNT   56  CEREBROVASC ACCID         2
AGE       COUNT   56                            2
COSTART   COUNT   58  HYPERTENS                 1
AGE       COUNT   58                            1
COSTART   COUNT   62  ANGINA PECTORIS           1
AGE       COUNT   62                            1
COSTART   COUNT   63  HYPERTENS                 1
AGE       COUNT   63                            1
COSTART   COUNT   64  SYNCOPE                   2
```

CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION
CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

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PPA CONTAINING DRUGS

```
-----------------------------------------------------------------------------------------
                 AGE          COSTART          TOTAL
                                            OCCURRENCES
-----------------------------------------------------------------------------------------
  CARDIOVASCULAR SYSTEM

AGE      COUNT    64                               2
COSTART  COUNT    67  BRADYCARDIA                  1
AGE      COUNT    67                               1
COSTART  COUNT    69  CEREBROVASC ACCID            1
AGE      COUNT    69                               1
COSTART  COUNT    71  HYPERTENS                    1
COSTART  COUNT    71  TACHYCARDIA                  1
AGE      COUNT    71                               2
COSTART  COUNT    72  ARRHYTHMIA                   1
COSTART  COUNT    72  HYPOTENS                     1
COSTART  COUNT    72  SYNCOPE                      1
AGE      COUNT    72                               3
COSTART  COUNT    73  ARRHYTHMIA VENT              1
AGE      COUNT    73                               1
COSTART  COUNT    80  BRADYCARDIA                  1
COSTART  COUNT    80  HYPOTENS                     1
AGE      COUNT    80                               2
-BODYCLAS COUNT                                   97

  DIGESTIVE SYSTEM
COSTART  COUNT        BEZOAR                       2
COSTART  COUNT        CONSTIP                      1
```

38 over age 55
28 over age 60
20 over age 65

```
 PPA CONTAINING DRUGS

--------------------------------------------------------------------------------------------------------
                AGE         COSTART          TOTAL
                                          OCCURRENCES
--------------------------------------------------------------------------------------------------------

 DIGESTIVE SYSTEM

COSTART  COUNT       DISCOLOR TOOTH             1

COSTART  COUNT       DRY MOUTH                  3

COSTART  COUNT       GASTRITIS HEM              1

COSTART  COUNT       GI DIS                     2

COSTART  COUNT       GLOSSITIS                  1

COSTART  COUNT       JAUNDICE                   1

COSTART  COUNT       NAUSEA                     6

COSTART  COUNT       NAUSEA VOMIT               6

COSTART  COUNT       RECTAL DIS                 1

COSTART  COUNT       STOMATITIS                 1

COSTART  COUNT       STOMATITIS ULCER           1

COSTART  COUNT       TOOTH CARIES               1

COSTART  COUNT       ULCER DUODEN HEM           1

AGE      COUNT                                 27

COSTART  COUNT    0  DRY MOUTH                  1

COSTART  COUNT    0  NECRO LIVER                1

AGE      COUNT    0                             2

COSTART  COUNT    1  JAUNDICE CHOLESTAT         1

AGE      COUNT    1                             1

COSTART  COUNT    3  VOMIT                      1

AGE      COUNT    3                             1
```

```
------------------------------------------------------------------------------------------
                 AGE         COSTART          TOTAL
                                           OCCURRENCES
------------------------------------------------------------------------------------------
 DIGESTIVE SYSTEM
COSTART  COUNT    4  NAUSEA                     1
AGE      COUNT    4                             1
COSTART  COUNT    6  DISCOLOR TOOTH             1
AGE      COUNT    6                             1
COSTART  COUNT    7  DYSPHAGIA                  2
COSTART  COUNT    7  JAUNDICE                   1
AGE      COUNT    7                             3
COSTART  COUNT   11  HYPER GUM                  1
AGE      COUNT   11                             1
COSTART  COUNT   13  PANCREATITIS               1
AGE      COUNT   13                             1
COSTART  COUNT   16  DIARRHEA                   1
COSTART  COUNT   16  JAUNDICE CHOLESTAT         1
COSTART  COUNT   16  NAUSEA VOMIT               1
AGE      COUNT   16                             3
COSTART  COUNT   18  EDEMA TONGUE               1
AGE      COUNT   18                             1
COSTART  COUNT   20  VOMIT                      1
AGE      COUNT   20                             1
COSTART  COUNT   21  LIVER FUNC ABNORM          1
AGE      COUNT   21                             1
COSTART  COUNT   22  PANCREATITIS               1
```

```
  PPA CONTAINING DRUGS

--------------------------------------------------------------------------------------------------
                AGE           COSTART           TOTAL
                                             OCCURRENCES
--------------------------------------------------------------------------------------------------

  DIGESTIVE SYSTEM

AGE      COUNT   22                                 1

COSTART  COUNT   25  NAUSEA                         1

AGE      COUNT   25                                 1

COSTART  COUNT   26  NAUSEA                         2

AGE      COUNT   26                                 2

COSTART  COUNT   27  NAUSEA VOMIT                   1

COSTART  COUNT   27  VOMIT                          1

AGE      COUNT   27                                 2

COSTART  COUNT   28  JAUNDICE                       1

COSTART  COUNT   28  STOMATITIS                     1

AGE      COUNT   28                                 2

COSTART  COUNT   29  DRY MOUTH                      1

AGE      COUNT   29                                 1

COSTART  COUNT   30  DRY MOUTH                      1

AGE      COUNT   30                                 1

COSTART  COUNT   39  THIRST                         1

AGE      COUNT   39                                 1

COSTART  COUNT   41  NAUSEA VOMIT                   1

COSTART  COUNT   41  VOMIT                          1

AGE      COUNT   41                                 2

COSTART  COUNT   42  HEM GI                         1
```

```
 PPA CONTAINING DRUGS

---------------------------------------------------------------------------------------------
                 AGE          COSTART           TOTAL
                                             OCCURRENCES
---------------------------------------------------------------------------------------------

 DIGESTIVE SYSTEM

AGE       COUNT   42                                1

COSTART   COUNT   45  INTEST PER                    1

AGE       COUNT   48                                1

COSTART   COUNT   49  DRY MOUTH                     1

COSTART   COUNT   49  DYSPEPSIA                     1

COSTART   COUNT   49  GLOSSITIS                     1

COSTART   COUNT   49  LIVER FUNC ABNORM             1

AGE       COUNT   49                                4

COSTART   COUNT   50  DRY MOUTH                     1

AGE       COUNT   50                                1

COSTART   COUNT   51  VOMIT                         1

AGE       COUNT   51                                1

COSTART   COUNT   53  DIARRHEA                      1

AGE       COUNT   53                                1

COSTART   COUNT   54  NAUSEA                        1

AGE       COUNT   54                                1

COSTART   COUNT   55  DYSPHAGIA                     2

AGE       COUNT   55                                2

COSTART   COUNT   58  HEM GI                        1

AGE       COUNT   58                                1

COSTART   COUNT   59  GI DIS                        1

AGE       COUNT   59                                1
```

```
  PPA CONTAINING DRUGS

-----------------------------------------------------------------------------------------------------
                 AGE          COSTART           TOTAL
                                            OCCURRENCES
-----------------------------------------------------------------------------------------------------

  DIGESTIVE SYSTEM

COSTART  COUNT  60  GI DIS                        1
COSTART  COUNT  60  SIALADENITIS                  1
AGE      COUNT  60                                2
COSTART  COUNT  61  JAUNDICE CHOLESTAT            1
COSTART  COUNT  61  NAUSEA                        1
AGE      COUNT  61                                2
COSTART  COUNT  62  DRY MOUTH                     1
AGE      COUNT  62                                1
COSTART  COUNT  64  NAUSEA                        1
AGE      COUNT  64                                1
COSTART  COUNT  65  NAUSEA VOMIT                  1
AGE      COUNT  65                                1
COSTART  COUNT  71  CONSTIP                       1
COSTART  COUNT  71  DIARRHEA                      1
AGE      COUNT  71                                2
COSTART  COUNT  74  NAUSEA VOMIT                  1
AGE      COUNT  74                                1
COSTART  COUNT  75  VOMIT                         1
AGE      COUNT  75                                1
COSTART  COUNT  84  JAUNDICE CHOLESTAT            1
AGE      COUNT  84                                1
```

583

```
  PPA CONTAINING DRUGS
------------------------------------------------------------------------------------------------------------------
                AGE          COSTART              TOTAL
                                              OCCURRENCES
------------------------------------------------------------------------------------------------------------------
  DIGESTIVE SYSTEM
COSTART  COUNT   85  DIARRHEA                     1
COSTART  COUNT   85  GASTRITIS                    1
COSTART  COUNT   85  HEM GI                       1
COSTART  COUNT   85  HEPATITIS                    1
AGE      COUNT   85                               4
COSTART  COUNT   89  ANOREXIA                     2
AGE      COUNT   89                               2
BODYCLAS COUNT                                   89

  ENDOCRINE SYSTEM
COSTART  COUNT       ADH INAPPROP                 1
COSTART  COUNT       HYPERTHYR                    1
AGE      COUNT                                    2
COSTART  COUNT    6  GOITER                       1
AGE      COUNT    6                               1
BODYCLAS COUNT                                    3

  HEMIC AND LYMPHATIC SYSTEM
COSTART  COUNT       AGRANULOCYTOSIS              1
COSTART  COUNT       ANEMIA APLAST                2
COSTART  COUNT       ANEMIA HEMOL                 1
COSTART  COUNT       ANEMIA IRON DEFIC            1
COSTART  COUNT       CYANOSIS                     1
```

44 over age 55
36 over age 60
24 over age 65

```
 PPA CONTAINING DRUGS
------------------------------------------------------------------------------------------------
                  AGE          COSTART            TOTAL
                                               OCCURRENCES
------------------------------------------------------------------------------------------------

 HEMIC AND LYMPHATIC SYSTEM

COSTART  COUNT        LEUKOCYTOSIS                1
COSTART  COUNT        LEUKOPENIA                  1
COSTART  COUNT        MARROW DEPRESS              1
COSTART  COUNT        MARROW HYPERPLASIA          1
COSTART  COUNT        PURPURA                     1
COSTART  COUNT        PURPURA THROMBOPEN          1
COSTART  COUNT        RBC ABNORM                  1
AGE      COUNT                                   13
COSTART  COUNT     1  PURPURA THROMBOPEN          1
AGE      COUNT     1                              1
COSTART  COUNT     2  INTRACRAN HYPERTENS         1
COSTART  COUNT     2  LEUKOPENIA                  1
COSTART  COUNT     2  THROMBOCYTOPENIA            3
AGE      COUNT     2                              5
COSTART  COUNT     3  THROMBOCYTOPENIA            1
AGE      COUNT     3                              1
COSTART  COUNT     4  THROMBOCYTOPENIA            1
AGE      COUNT     4                              1
COSTART  COUNT    16  THROMBOCYTOPENIA            1
AGE      COUNT    16                              1
COSTART  COUNT    18  CYANOSIS                    1
```

PPA CONTAINING DRUGS

		AGE	COSTART	TOTAL OCCURRENCES
HEMIC AND LYMPHATIC SYSTEM				
AGE	COUNT	18		1
COSTART	COUNT	32	ANEMIA	1
AGE	COUNT	32		1
COSTART	COUNT	35	AGRANULOCYTOSIS	1
AGE	COUNT	35		1
COSTART	COUNT	41	ANEMIA APLAST	2
COSTART	COUNT	41	ECCHYMOSIS	1
AGE	COUNT	41		3
COSTART	COUNT	49	EOSINOPHILIA	2
COSTART	COUNT	49	LEUKOPENIA	1
AGE	COUNT	49		3
COSTART	COUNT	50	ANEMIA IRON DEFIC	1
AGE	COUNT	50		1
COSTART	COUNT	55	THROMBOCYTHEM	1
AGE	COUNT	55		1
COSTART	COUNT	62	PURPURA	1
AGE	COUNT	62		1
COSTART	COUNT	66	ANEMIA	1
AGE	COUNT	66		1
COSTART	COUNT	69	THROMBOCYTOPENIA	1
AGE	COUNT	69		1
COSTART	COUNT	76	PURPURA	1

```
  PPA CONTAINING DRUGS

-----------------------------------------------------------------------------------------------------------------------------------
               AGE          COSTART           TOTAL
                                           OCCURRENCES
-----------------------------------------------------------------------------------------------------------------------------------

  HEMIC AND LYMPHATIC SYSTEM

AGE      COUNT   76                               1

COSTART  COUNT   85  MARROW DEPRESS               1

AGE      COUNT   85                               1

BODYCLAS COUNT                                   38

  METABOLIC AND NUTRITIONAL DISORDERS

COSTART  COUNT       ANEMIA IRON DEFIC            1

COSTART  COUNT       CYANOSIS                     1

COSTART  COUNT       EDEMA                        1

COSTART  COUNT       GLYCOSURIA                   1

COSTART  COUNT       HYPOGLYCEM                   1

COSTART  COUNT       SGOT INC                     2

AGE      COUNT                                    7

COSTART  COUNT    7  GROWTH RETARD                1

AGE      COUNT    7                               1

COSTART  COUNT   11  HYPERURICEM                  1

AGE      COUNT   11                               1

COSTART  COUNT   12  GROWTH RETARD                1

AGE      COUNT   12                               1

COSTART  COUNT   13  CREATINE PK INC              1

COSTART  COUNT   13  HYPERGLYCEM                  1

AGE      COUNT   13                               2
```

12 over age 55
10 over age 60
8 over age 65

```
  PPA CONTAINING DRUGS

---------------------------------------------------------------------------------
                 AGE          COSTART          TOTAL
                                            OCCURRENCES
---------------------------------------------------------------------------------

  METABOLIC AND NUTRITIONAL DISORDERS

COSTART  COUNT   15  EDEMA PERIPH                1
AGE      COUNT   15                              1
COSTART  COUNT   18  CYANOSIS                    1
AGE      COUNT   18                              1
COSTART  COUNT   20  EDEMA                       1
COSTART  COUNT   20  SGOT INC                    1
AGE      COUNT   20                              2
COSTART  COUNT   22  CREATINE PK INC             1
AGE      COUNT   22                              1
COSTART  COUNT   23  ALBUMINURIA                 1
AGE      COUNT   23                              1
COSTART  COUNT   24  EDEMA                       2
COSTART  COUNT   24  HYPOGLYCEM                  1
AGE      COUNT   24                              3
COSTART  COUNT   25  DIABETES MELL               1
AGE      COUNT   25                              1
COSTART  COUNT   34  ACIDOSIS                    1
AGE      COUNT   34                              1
COSTART  COUNT   38  SGOT INC                    1
COSTART  COUNT   38  SGPT INC                    1
AGE      COUNT   38                              2
```

```
  PPA CONTAINING DRUGS

--------------------------------------------------------------------------------------------------
                AGE         COSTART          TOTAL
                                          OCCURRENCES
--------------------------------------------------------------------------------------------------

  METABOLIC AND NUTRITIONAL DISORDERS

COSTART  COUNT   39  THIRST                    1

AGE      COUNT   39                            1

COSTART  COUNT   43  EDEMA                     1

AGE      COUNT   43                            1

COSTART  COUNT   44  HYPOGLYCEM                1

AGE      COUNT   44                            1

COSTART  COUNT   46  HYPERKALEM                1

AGE      COUNT   46                            1

COSTART  COUNT   48  GOUT                      1

COSTART  COUNT   48  HYPONATRE I               1

AGE      COUNT   48                            2

COSTART  COUNT   49  EDEMA PERIPH              1

COSTART  COUNT   49  WEIGHT INC                1

AGE      COUNT   49                            2

COSTART  COUNT   50  ANEMIA IRON DEFIC         1

AGE      COUNT   50                            1

COSTART  COUNT   68  HYPERGLYCEM               1

COSTART  COUNT   68  SGOT INC                  1

AGE      COUNT   68                            2

COSTART  COUNT   84  WEIGHT DEC                1

AGE      COUNT   84                            1

BODYCLAS COUNT                                37
```

5 over 65

582

```
 PPA CONTAINING DRUGS
-----------------------------------------------------------------------------------------------------------
                AGE       COSTART          TOTAL
                                        OCCURRENCES
-----------------------------------------------------------------------------------------------------------
 METABOLIC AND NUTRITIONAL DISORDERS


 MUSCULOSKELETAL SYSTEM
COSTART  COUNT        ARTHRALGIA             1
COSTART  COUNT        MYOSITIS               1
AGE      COUNT                               2
COSTART  COUNT     2  ARTHRALGIA             1
AGE      COUNT     2                         1
COSTART  COUNT     3  ARTHRITIS              1
AGE      COUNT     3                         1
COSTART  COUNT     6  ARTHRITIS              1
AGE      COUNT     6                         1
COSTART  COUNT    20  TETANY                 1
AGE      COUNT    20                         1
COSTART  COUNT    22  MYALGIA                1
AGE      COUNT    22                         1
COSTART  COUNT    26  TETANY                 1
AGE      COUNT    26                         1
COSTART  COUNT    55  ARTHRALGIA             1
COSTART  COUNT    55  ARTHRITIS              1
AGE      COUNT    55                         2
COSTART  COUNT    56  ARTHRALGIA             1
AGE      COUNT    56                         1
```

6 over 55

```
  PPA CONTAINING DRUGS

-------------------------------------------------------------------------------------------------
                AGE        COSTART          TOTAL
                                         OCCURRENCES
-------------------------------------------------------------------------------------------------

  MUSCULOSKELETAL SYSTEM

BODYCLAS COUNT                              11

  NERVOUS SYSTEM
COSTART  COUNT       ADRENERG SYND           1
COSTART  COUNT       AGITATION               2
COSTART  COUNT       AMNESIA                 2
COSTART  COUNT       ANOMALY CONGEN CNS      1
COSTART  COUNT       ANTICHOLINERG SYND      1
COSTART  COUNT       CEREBROVASC ACCID       2
COSTART  COUNT       CNS STIMULAT            2
COSTART  COUNT       CONFUS                  4
COSTART  COUNT       CONVULS                 1
COSTART  COUNT       DELUSIONS               1
COSTART  COUNT       DEMENTIA                1
COSTART  COUNT       DEPERSONAL              1
COSTART  COUNT       DEPRESSION              2
COSTART  COUNT       DIZZINESS               5
COSTART  COUNT       DRUG DEPEND             1
COSTART  COUNT       DRY MOUTH               3
COSTART  COUNT       EMOTION LABIL           1
COSTART  COUNT       EUPHORIA                1
COSTART  COUNT       HALLUCIN                9
```

CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION
CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

PPA CONTAINING DRUGS

```
-------------------------------------------------------------------------------------------
                 AGE         COSTART          TOTAL
                                           OCCURRENCES
-------------------------------------------------------------------------------------------
 NERVOUS SYSTEM

COSTART  COUNT       HYPERTENS                 3
COSTART  COUNT       INSOMNIA                  2
COSTART  COUNT       MANIC REACT               1
COSTART  COUNT       NERVOUSNESS               4
COSTART  COUNT       NEURITIS RETROBULBAR      1
COSTART  COUNT       OCULOGYRIC CRISIS         1
COSTART  COUNT       PARALYSIS                 1
COSTART  COUNT       PARANOID REACT            1
COSTART  COUNT       PERSON DIS                1
COSTART  COUNT       PSYCHOSIS                 1
COSTART  COUNT       SCHIZOPHRENIC REACT       1
COSTART  COUNT       SOMNOLENCE                5
COSTART  COUNT       SPEECH DIS                1
COSTART  COUNT       URIN RETENT               9
COSTART  COUNT       VASODILAT                 1
COSTART  COUNT       VERTIGO                   1
AGE      COUNT                                75
COSTART  COUNT    0  DIZZINESS                 1
COSTART  COUNT    0  DRY MOUTH                 1
COSTART  COUNT    0  OPISTHOTONOS              1
COSTART  COUNT    0  THROM CEREBR              1
```

```
------------------------------------------------------------------------------------------------
                    AGE         COSTART          TOTAL
                                              OCCURRENCES
------------------------------------------------------------------------------------------------

 NERVOUS SYSTEM

AGE      COUNT    0                              4
COSTART  COUNT    1  CONVULS                     1
COSTART  COUNT    1  CONVULS GRAND MAL           1
COSTART  COUNT    1  HYPERKINESIA                1
COSTART  COUNT    1  INSOMNIA                    1
COSTART  COUNT    1  INTRACRAN HYPERTENS         2
COSTART  COUNT    1  PERSON DIS                  1
AGE      COUNT    1                              7
COSTART  COUNT    2  COORDINAT ABNORM            1
COSTART  COUNT    2  HALLUCIN                    1
COSTART  COUNT    2  HYPERKINESIA                4
COSTART  COUNT    2  INTRACRAN HYPERTENS         1
COSTART  COUNT    2  NERVOUSNESS                 3
COSTART  COUNT    2  SOMNOLENCE                  1
AGE      COUNT    2                             11
COSTART  COUNT    3  CONVULS GRAND MAL           1
COSTART  COUNT    3  HYPERKINESIA                2
COSTART  COUNT    3  INSOMNIA                    1
COSTART  COUNT    3  PERSON DIS                  1
COSTART  COUNT    3  SOMNOLENCE                  1
AGE      COUNT    3                              6
COSTART  COUNT    4  CNS STIMULAT                1
```

```
  PPA CONTAINING DRUGS

-------------------------------------------------------------------------------------------
                    AGE        COSTART          TOTAL
                                             OCCURRENCES
-------------------------------------------------------------------------------------------

  NERVOUS SYSTEM

COSTART  COUNT    4  EXTRAPYR SYND               1
COSTART  COUNT    4  HALLUCIN                    2
COSTART  COUNT    4  HYPERKINESIA                2
COSTART  COUNT    4  OCULOGYRIC CRISIS           1
COSTART  COUNT    4  SOMNOLENCE                  2
AGE      COUNT    4                              9
COSTART  COUNT    5  DREAM ABNORM                1
COSTART  COUNT    5  MENTAL RETARD               1
COSTART  COUNT    5  NEUROPATHY                  1
AGE      COUNT    5                              3
COSTART  COUNT    6  HALLUCIN                    1
COSTART  COUNT    6  HYPERKINESIA                1
AGE      COUNT    6                              2
COSTART  COUNT    7  CONVULS GRAND MAL           1
COSTART  COUNT    7  DEPRESSION                  1
COSTART  COUNT    7  EXTRAPYR SYND               1
COSTART  COUNT    7  HALLUCIN                    1
COSTART  COUNT    7  NERVOUSNESS                 1
AGE      COUNT    7                              5
COSTART  COUNT    8  NERVOUSNESS                 1
AGE      COUNT    8                              1
```

```
 PPA CONTAINING DRUGS

----------------------------------------------------------------------------------------------------
                 AGE        COSTART          TOTAL
                                          OCCURRENCES
----------------------------------------------------------------------------------------------------

 NERVOUS SYSTEM
COSTART  COUNT   11  SOMNOLENCE                 1
AGE      COUNT   11                             1
COSTART  COUNT   12  HYPERTENS                  1
AGE      COUNT   12                             1
COSTART  COUNT   13  CNS STIMULAT               1
COSTART  COUNT   13  HYPERTENS                  1
AGE      COUNT   13                             2
COSTART  COUNT   14  CONVULS                    2
AGE      COUNT   14                             2
COSTART  COUNT   15  SOMNOLENCE                 1
AGE      COUNT   15                             1
COSTART  COUNT   17  HALLUCIN                   1
COSTART  COUNT   17  PARESTHESIA                1
COSTART  COUNT   17  SOMNOLENCE                 2
AGE      COUNT   17                             4
COSTART  COUNT   18  DIZZINESS                  2
COSTART  COUNT   18  DYSARTHRIA                 1
COSTART  COUNT   18  SOMNOLENCE                 1
COSTART  COUNT   18  STUPOR                     1
COSTART  COUNT   18  TORTICOLLIS                1
AGE      COUNT   18                             6
COSTART  COUNT   19  SOMNOLENCE                 1
```

```
 PPA CONTAINING DRUGS

--------------------------------------------------------------------------------------------
                    AGE          COSTART             TOTAL
                                                   OCCURRENCES
--------------------------------------------------------------------------------------------

 NERVOUS SYSTEM

AGE      COUNT   19                                  1
COSTART  COUNT   20  COMA                            1
COSTART  COUNT   20  HYPERTENS                       2
COSTART  COUNT   20  SOMNOLENCE                      1
AGE      COUNT   20                                  4
COSTART  COUNT   22  COORDINAT ABNORM                1
COSTART  COUNT   22  DIZZINESS                       1
COSTART  COUNT   22  HYPERTENS                       2
COSTART  COUNT   22  SOMNOLENCE                      1
AGE      COUNT   22                                  5
COSTART  COUNT   23  HALLUCIN                        1
COSTART  COUNT   23  NYSTAGMUS                       1
COSTART  COUNT   23  SOMNOLENCE                      1
COSTART  COUNT   23  URIN RETENT                     1
AGE      COUNT   23                                  4
COSTART  COUNT   24  CONVULS                         1
COSTART  COUNT   24  CONVULS GRAND MAL               1
COSTART  COUNT   24  DEPRESSION                      1
COSTART  COUNT   24  NERVOUSNESS                     1
COSTART  COUNT   24  SOMNOLENCE                      1
AGE      COUNT   24                                  5
```

PPA CONTAINING DRUGS

```
-------------------------------------------------------------------------------------------------
                 AGE          COSTART          TOTAL
                                            OCCURRENCES
-------------------------------------------------------------------------------------------------

 NERVOUS SYSTEM

COSTART  COUNT   25  ATAXIA                         1
COSTART  COUNT   25  CONVULS                        1
COSTART  COUNT   25  DIZZINESS                      1
COSTART  COUNT   25  HALLUCIN                       1
COSTART  COUNT   25  HYPERTENS                      1
COSTART  COUNT   25  NERVOUSNESS                    1
COSTART  COUNT   25  SOMNOLENCE                     1
COSTART  COUNT   25  TORTICOLLIS                    1
AGE      COUNT   25                                 8
COSTART  COUNT   26  ANXIETY                        1
COSTART  COUNT   26  ATAXIA                         1
COSTART  COUNT   26  DIZZINESS                      1
COSTART  COUNT   26  EMOTION LABIL                  1
COSTART  COUNT   26  HEM INTRACRAN                  1
COSTART  COUNT   26  HYPERTENS                      3
COSTART  COUNT   26  PARESTHESIA                    2
COSTART  COUNT   26  SOMNOLENCE                     1
AGE      COUNT   26                                11
COSTART  COUNT   27  ANTICHOLINERG SYND             1
COSTART  COUNT   27  HYPERTENS                      3
COSTART  COUNT   27  NEURITIS PERIPH                1
AGE      COUNT   27                                 5
```

```
 PPA CONTAINING DRUGS
--------------------------------------------------------------------------------------------------------------------------------
               AGE         COSTART          TOTAL
                                         OCCURRENCES
--------------------------------------------------------------------------------------------------------------------------------
 NERVOUS SYSTEM

COSTART  COUNT   28  DIZZINESS                   1
COSTART  COUNT   28  NYSTAGMUS                   1
COSTART  COUNT   28  SOMNOLENCE                  2
COSTART  COUNT   28  SPEECH DIS                  1
AGE      COUNT   28                              5
COSTART  COUNT   29  COORDINAT ABNORM            1
COSTART  COUNT   29  DEPRESSION                  1
COSTART  COUNT   29  DRY MOUTH                   1
COSTART  COUNT   29  EUPHORIA                    1
COSTART  COUNT   29  SOMNOLENCE                  1
AGE      COUNT   29                              5
COSTART  COUNT   30  ANXIETY                     1
COSTART  COUNT   30  CONVULS GRAND MAL           1
COSTART  COUNT   30  DIZZINESS                   1
COSTART  COUNT   30  DRY MOUTH                   1
AGE      COUNT   30                              4
COSTART  COUNT   31  HYPERTENS                   1
COSTART  COUNT   31  PARESTHESIA                 1
COSTART  COUNT   31  SOMNOLENCE                  1
AGE      COUNT   31                              3
COSTART  COUNT   32  CONVULS                     1
```

PPA CONTAINING DRUGS

		AGE	COSTART	TOTAL OCCURRENCES
NERVOUS SYSTEM				
COSTART	COUNT	32	HEM INTRACRAN	1
COSTART	COUNT	32	HYPERTENS	1
COSTART	COUNT	32	HYPERTONIA	1
COSTART	COUNT	32	SOMNOLENCE	2
AGE	COUNT	32		5
COSTART	COUNT	33	HALLUCIN	1
COSTART	COUNT	33	HYPERTENS	1
COSTART	COUNT	33	SOMNOLENCE	1
AGE	COUNT	33		3
COSTART	COUNT	34	CONVULS	1
COSTART	COUNT	34	DIZZINESS	1
COSTART	COUNT	34	HYPERTENS	1
AGE	COUNT	34		3
COSTART	COUNT	35	HALLUCIN	1
COSTART	COUNT	35	SOMNOLENCE	2
AGE	COUNT	35		3
COSTART	COUNT	36	HEM INTRACRAN	1
COSTART	COUNT	36	STUPOR	1
AGE	COUNT	36		2
COSTART	COUNT	37	ATAXIA	1
AGE	COUNT	37		1
COSTART	COUNT	38	DIZZINESS	1

PPA CONTAINING DRUGS

		AGE	COSTART	TOTAL OCCURRENCES
NERVOUS SYSTEM				
COSTART	COUNT	38	DREAM ABNORM	1
COSTART	COUNT	38	DRUG DEPEND	1
COSTART	COUNT	38	HYPERTENS	1
COSTART	COUNT	38	VASODILAT	1
COSTART	COUNT	38	WITHDRAW SYND	1
AGE	COUNT	38		6
COSTART	COUNT	39	SOMNOLENCE	1
COSTART	COUNT	39	URIN RETENT	1
COSTART	COUNT	39	VESTIBUL DIS	1
AGE	COUNT	39		3
COSTART	COUNT	40	HEM INTRACRAN	1
COSTART	COUNT	40	SOMNOLENCE	1
AGE	COUNT	40		2
COSTART	COUNT	41	SOMNOLENCE	1
COSTART	COUNT	41	URIN RETENT	1
AGE	COUNT	41		2
COSTART	COUNT	42	CONFUS	1
COSTART	COUNT	42	COORDINAT ABNORM	1
AGE	COUNT	42		2
COSTART	COUNT	43	HALLUCIN	1
COSTART	COUNT	43	PARESTHESIA	1

```
 PPA CONTAINING DRUGS
------------------------------------------------------------------------------------------
                  AGE          COSTART          TOTAL
                                             OCCURRENCES
------------------------------------------------------------------------------------------

 NERVOUS SYSTEM
AGE       COUNT   43                               2
COSTART   COUNT   44  CEREBROVASC DIS              1
COSTART   COUNT   44  HYPERTENS                    1
AGE       COUNT   44                               2
COSTART   COUNT   45  HYPERTENS                    1
AGE       COUNT   45                               1
COSTART   COUNT   46  SOMNOLENCE                   1
AGE       COUNT   46                               1
COSTART   COUNT   47  HEM INTRACRAN                1
COSTART   COUNT   47  HYPERTENS                    1
AGE       COUNT   47                               2
COSTART   COUNT   48  BRAIN SYND ACUTE             1
COSTART   COUNT   48  COMA                         1
COSTART   COUNT   48  DIZZINESS                    1
COSTART   COUNT   48  HYPERTENS                    2
AGE       COUNT   48                               5
COSTART   COUNT   49  DRY MOUTH                    1
COSTART   COUNT   49  INTRACRAN HYPERTENS          1
AGE       COUNT   49                               2
COSTART   COUNT   50  DRY MOUTH                    1
COSTART   COUNT   50  PSYCHOSIS                    1
COSTART   COUNT   50  SOMNOLENCE                   1
```

```
 PPA CONTAINING DRUGS

--------------------------------------------------------------------------------------------------------
                 AGE         COSTART          TOTAL
                                           OCCURRENCES
--------------------------------------------------------------------------------------------------------

 NERVOUS SYSTEM

AGE      COUNT   50                              3
COSTART  COUNT   51  DELUSIONS                   1
COSTART  COUNT   51  ENCEPHALOP HYPERTENS        1
COSTART  COUNT   51  HALLUCIN                    2
AGE      COUNT   51                              4
COSTART  COUNT   52  DIZZINESS                   1
COSTART  COUNT   52  SOMNOLENCE                  1
AGE      COUNT   52                              2
COSTART  COUNT   53  DIZZINESS                   1
AGE      COUNT   53                              1
COSTART  COUNT   55  CEREBROVASC ACCID           1
COSTART  COUNT   55  INSOMNIA                    1
COSTART  COUNT   55  NERVOUSNESS                 1
COSTART  COUNT   55  URIN RETENT                 1
AGE      COUNT   55                              4
COSTART  COUNT   56  CEREBROVASC ACCID           2
COSTART  COUNT   56  PARALYSIS                   2
AGE      COUNT   56                              4
COSTART  COUNT   57  URIN RETENT                 1
AGE      COUNT   57                              1
COSTART  COUNT   58  HYPERTENS                   1
```

```
  PPA CONTAINING DRUGS

------------------------------------------------------------------------------------------------------------------------------------
                AGE         COSTART           TOTAL
                                           OCCURRENCES
------------------------------------------------------------------------------------------------------------------------------------

  NERVOUS SYSTEM

AGE       COUNT   58                                1

COSTART   COUNT   60  DIZZINESS                     1

COSTART   COUNT   60  HEMIPLEGIA                    1

COSTART   COUNT   60  HYPERTENS                     1

AGE       COUNT   60                                3

COSTART   COUNT   61  AMNESIA                       1

COSTART   COUNT   61  DIZZINESS                     1

COSTART   COUNT   61  SOMNOLENCE                    1

AGE       COUNT   61                                3

COSTART   COUNT   62  DEPRESSION                    1

COSTART   COUNT   62  DRY MOUTH                     1

COSTART   COUNT   62  URIN RETENT                   1

AGE       COUNT   62                                3

COSTART   COUNT   63  COMA                          1

COSTART   COUNT   63  HYPERTENS                     1

AGE       COUNT   63                                2

COSTART   COUNT   66  CONFUS                        1

COSTART   COUNT   66  HOSTILITY                     1

COSTART   COUNT   65  HYPERTENS                     1

COSTART   COUNT   66  URIN RETENT                   1

AGE       COUNT   66                                4

COSTART   COUNT   67  SOMNOLENCE                    1
```

```
  PPA CONTAINING DRUGS

------------------------------------------------------------------------------------------------------------
                 AGE          COSTART           TOTAL
                                             OCCURRENCES
------------------------------------------------------------------------------------------------------------

  NERVOUS SYSTEM

COSTART  COUNT   67  STUPOR                       1
AGE      COUNT   67                               2
COSTART  COUNT   69  CEREBROVASC ACCID            1
AGE      COUNT   69                               1
COSTART  COUNT   70  BRAIN SYND ACUTE             1
COSTART  COUNT   70  URIN RETENT                  1
AGE      COUNT   70                               2
COSTART  COUNT   71  HYPERTENS                    1
COSTART  COUNT   71  TORTICOLLIS                  1
COSTART  COUNT   71  TREMOR                       1
AGE      COUNT   71                               3
COSTART  COUNT   75  AMNESIA                      1
COSTART  COUNT   75  DIZZINESS                    1
COSTART  COUNT   75  SOMNOLENCE                   2
AGE      COUNT   75                               4
COSTART  COUNT   77  URIN RETENT                  1
AGE      COUNT   77                               1
COSTART  COUNT   81  URIN RETENT                  1
AGE      COUNT   81                               1
COSTART  COUNT   88  TREMOR                       1
AGE      COUNT   88                               1
```

3011

```
PPA CONTAINING DRUGS

-------------------------------------------------------------------------------
                 AGE          COSTART          TOTAL
                                             OCCURRENCES
-------------------------------------------------------------------------------

  NERVOUS SYSTEM

COSTART  COUNT   89  CONFUS                     2
AGE      COUNT   89                             2
BODYCLAS COUNT                                300

  RESPIRATORY SYSTEM

COSTART  COUNT       ASTHMA                     2
COSTART  COUNT       BRONCHITIS                 2
COSTART  COUNT       HICCUP                     1
COSTART  COUNT       LARYNGITIS                 1
COSTART  COUNT       PHARYNGITIS                1
COSTART  COUNT       PNEUMONIA                  1
COSTART  COUNT       RHINITIS                   2
COSTART  COUNT       SINUSITIS                  4
AGE      COUNT                                 14
COSTART  COUNT    2  HYPERVENTIL                1
AGE      COUNT    2                             1
COSTART  COUNT   13  DYSPNEA                    1
AGE      COUNT   13                             1
COSTART  COUNT   14  DYSPNEA                    1
AGE      COUNT   14                             1
COSTART  COUNT   16  DYSPNEA                    1
AGE      COUNT   16                             1
```

84 over age 55
64 over age 60
42 over age 65

```
06/21/83                              CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION                    PAGE 99
                                        CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES
 PPA CONTAINING DRUGS
------------------------------------------------------------------------------------------------------------------------
                 AGE          COSTART           TOTAL
                                             OCCURRENCES
------------------------------------------------------------------------------------------------------------------------
 RESPIRATORY SYSTEM
COSTART   COUNT   18  HYPERVENTIL                 1
COSTART   COUNT   18  HYPOVENTIL                  1
AGE       COUNT   18                              2
COSTART   COUNT   19  APNEA                       1
AGE       COUNT   19                              1
COSTART   COUNT   21  APNEA                       1
AGE       COUNT   21                              1
COSTART   COUNT   22  EDEMA LUNG                  1
AGE       COUNT   22                              1
COSTART   COUNT   28  PHARYNGITIS                 1
AGE       COUNT   28                              1
COSTART   COUNT   29  RHINITIS                    1
AGE       COUNT   29                              1
COSTART   COUNT   30  ASTHMA                      1
COSTART   COUNT   30  BRONCHITIS                  2
AGE       COUNT   30                              3
COSTART   COUNT   32  DYSPNEA                     1
COSTART   COUNT   32  RHINITIS                    1
AGE       COUNT   32                              2
COSTART   COUNT   33  HYPERVENTIL                 1
COSTART   COUNT   33  RHINITIS                    1
AGE       COUNT   33                              2
```

```
06/21/83                         CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION                    PAGE 100
                                    CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES
  PPA CONTAINING DRUGS

----------------------------------------------------------------------------------------------------------------------
                   AGE          COSTART          TOTAL
                                              OCCURRENCES
----------------------------------------------------------------------------------------------------------------------

  RESPIRATORY SYSTEM

COSTART  COUNT   38  DYSPNEA                     1
AGE      COUNT   38                              1
COSTART  COUNT   41  EPISTAXIS                   1
AGE      COUNT   41                              1
COSTART  COUNT   43  DYSPNEA                     1
AGE      COUNT   43                              1
COSTART  COUNT   53  EDEMA LUNG                  1
AGE      COUNT   53                              1
COSTART  COUNT   55  DYSPNEA                     1
AGE      COUNT   55                              1
COSTART  COUNT   58  DYSPNEA                     1
COSTART  COUNT   58  PNEUMONIA                   1
COSTART  COUNT   58  RHINITIS                    1
AGE      COUNT   58                              3
COSTART  COUNT   60  EPISTAXIS                   1
AGE      COUNT   60                              1
COSTART  COUNT   63  RHINITIS                    1
AGE      COUNT   63                              1
COSTART  COUNT   67  EPISTAXIS                   1
AGE      COUNT   67                              1
COSTART  COUNT   70  ASTHMA                      1
```

```
PPA CONTAINING DRUGS
-------------------------------------------------------------------------------------------
                 AGE         COSTART          TOTAL
                                           OCCURRENCES
-------------------------------------------------------------------------------------------
  RESPIRATORY SYSTEM
COSTART  COUNT   70  DYSPNEA                    1
AGE      COUNT   70                             2
BODYCLAS COUNT                                 45

  SKIN AND APPENDAGES
COSTART  COUNT       ACNE                       1
COSTART  COUNT       ALOPECIA                   3
COSTART  COUNT       DERM EXFOL                 1
COSTART  COUNT       ERYTHEMA MULT              3
COSTART  COUNT       RASH                      13
COSTART  COUNT       RASH MAC PAP               4
COSTART  COUNT       RASH PUST                  1
COSTART  COUNT       RASH VESIC BULL            2
COSTART  COUNT       STEVENS JOHNSON SYND       1
COSTART  COUNT       SWEAT                      3
COSTART  COUNT       URTICARIA                  6
AGE      COUNT                                 38
COSTART  COUNT    0  RASH MAC PAP               1
AGE      COUNT    0                             1
COSTART  COUNT    1  ERYTHEMA MULT              1
COSTART  COUNT    1  RASH                       1
AGE      COUNT    1                             2
```

18 over age 55
10 over age 60
8 over age 65

```
 PPA CONTAINING DRUGS
----------------------------------------------------------------------------------------------------------
                  AGE          COSTART           TOTAL
                                              OCCURRENCES
----------------------------------------------------------------------------------------------------------

 SKIN AND APPENDAGES

COSTART   COUNT     2  ERYTHEMA MULT              1

COSTART   COUNT     2  PRURITUS                   1

COSTART   COUNT     2  RASH                       2

COSTART   COUNT     2  RASH MAC PAP               1

COSTART   COUNT     2  STEVENS JOHNSON SYND       1

COSTART   COUNT     2  URTICARIA                  1

AGE       COUNT     2                             7

COSTART   COUNT     3  ERYTHEMA MULT              1

COSTART   COUNT     3  PRURITUS                   1

COSTART   COUNT     3  RASH MAC PAP               1

COSTART   COUNT     3  RASH PETECH                1

AGE       COUNT     3                             4

COSTART   COUNT     4  ERYTHEMA MULT              1

AGE       COUNT     4                             1

COSTART   COUNT     6  PRURITUS                   1

COSTART   COUNT     6  RASH                       1

COSTART   COUNT     6  RASH VESIC BULL            1

COSTART   COUNT     6  STEVENS JOHNSON SYND       1

AGE       COUNT     6                             4

COSTART   COUNT     8  SWEAT                      1

AGE       COUNT     8                             1

COSTART   COUNT    14  ERYTHEMA MULT              1
```

```
 PPA CONTAINING DRUGS
--------------------------------------------------------------------------
                 AGE        COSTART          TOTAL
                                          OCCURRENCES
--------------------------------------------------------------------------

 SKIN AND APPENDAGES

COSTART  COUNT  14  URTICARIA                   1
AGE      COUNT  14                              2
COSTART  COUNT  15  RASH                        1
COSTART  COUNT  15  URTICARIA                   1
AGE      COUNT  15                              2
COSTART  COUNT  16  ANGIOEDEMA                  1
COSTART  COUNT  16  RASH                        1
COSTART  COUNT  16  URTICARIA                   1
AGE      COUNT  16                              3
COSTART  COUNT  19  RASH                        1
COSTART  COUNT  19  URTICARIA                   1
AGE      COUNT  19                              2
COSTART  COUNT  21  RASH                        2
COSTART  COUNT  21  RASH VESIC BULL             1
COSTART  COUNT  21  URTICARIA                   1
AGE      COUNT  21                              4
COSTART  COUNT  22  URTICARIA                   2
AGE      COUNT  22                              2
COSTART  COUNT  23  EPIDERM NECRO               1
AGE      COUNT  23                              1
COSTART  COUNT  24  RASH                        1
```

```
  PPA CONTAINING DRUGS

--------------------------------------------------------------------------------------------------
                    AGE          COSTART            TOTAL
                                                 OCCURRENCES
--------------------------------------------------------------------------------------------------

  SKIN AND APPENDAGES

COSTART   COUNT    24   URTICARIA                     2
AGE       COUNT    24                                 3
COSTART   COUNT    26   PRURITUS                      1
COSTART   COUNT    26   RASH MAC PAP                  1
AGE       COUNT    26                                 2
COSTART   COUNT    27   RASH                          1
COSTART   COUNT    27   SWEAT                         1
AGE       COUNT    27                                 2
COSTART   COUNT    28   RASH                          2
COSTART   COUNT    28   RASH MAC PAP                  1
COSTART   COUNT    28   SKIN DISCOLOR                 1
COSTART   COUNT    28   URTICARIA                     2
AGE       COUNT    28                                 6
COSTART   COUNT    29   RASH                          1
AGE       COUNT    29                                 1
COSTART   COUNT    30   ERYTHEMA MULT                 1
AGE       COUNT    30                                 1
COSTART   COUNT    31   PRURITUS                      1
COSTART   COUNT    31   RASH MAC PAP                  1
COSTART   COUNT    31   URTICARIA                     1
AGE       COUNT    31                                 3
COSTART   COUNT    33   RASH                          2
```

PPA CONTAINING DRUGS

```
--------------------------------------------------------------------------------------------------------
                 AGE          COSTART           TOTAL
                                             OCCURRENCES
--------------------------------------------------------------------------------------------------------

 SKIN AND APPENDAGES

COSTART   COUNT   33  URTICARIA                   1

AGE       COUNT   33                              3

COSTART   COUNT   34  PRURITUS                    1

COSTART   COUNT   34  RASH                        1

COSTART   COUNT   34  URTICARIA                   1

AGE       COUNT   34                              3

COSTART   COUNT   35  ANGIOEDEMA                  1

COSTART   COUNT   35  PRURITUS                    1

COSTART   COUNT   35  RASH                        1

COSTART   COUNT   35  URTICARIA                   2

AGE       COUNT   35                              5

COSTART   COUNT   36  RASH MAC PAP                2

AGE       COUNT   36                              2

COSTART   COUNT   37  ERYTHEMA MULT               1

COSTART   COUNT   37  URTICARIA                   1

AGE       COUNT   37                              2

COSTART   COUNT   40  ANGIOEDEMA                  1

AGE       COUNT   40                              1

COSTART   COUNT   43  RASH                        1

COSTART   COUNT   43  URTICARIA                   2

AGE       COUNT   43                              3
```

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CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION
CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

PPA CONTAINING DRUGS

SKIN AND APPENDAGES

		AGE	COSTART	TOTAL OCCURRENCES
COSTART	COUNT	44	URTICARIA	1
AGE	COUNT	44		1
COSTART	COUNT	45	URTICARIA	1
AGE	COUNT	45		1
COSTART	COUNT	46	PRURITUS	1
COSTART	COUNT	46	RASH MAC PAP	1
COSTART	COUNT	46	RASH VESIC BULL	1
AGE	COUNT	46		3
COSTART	COUNT	48	RASH MAC PAP	1
COSTART	COUNT	48	URTICARIA	1
AGE	COUNT	48		2
COSTART	COUNT	49	NAIL DIS	1
COSTART	COUNT	49	RASH	1
COSTART	COUNT	49	URTICARIA	1
AGE	COUNT	49		3
COSTART	COUNT	51	RASH MAC PAP	1
AGE	COUNT	51		1
COSTART	COUNT	53	ANGIOEDEMA	1
COSTART	COUNT	53	PRURITUS	1
COSTART	COUNT	53	RASH	1
AGE	COUNT	53		3
COSTART	COUNT	55	EPIDERM NECRO	1

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```
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                           CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES
 PPA CONTAINING DRUGS
-----------------------------------------------------------------------------------------------------------
                AGE         COSTART             TOTAL
                                             OCCURRENCES
-----------------------------------------------------------------------------------------------------------

 SKIN AND APPENDAGES

COSTART  COUNT   55  RASH MAC PAP                 1
COSTART  COUNT   55  URTICARIA                    1
AGE      COUNT   55                               3
COSTART  COUNT   61  NAIL DIS                     1
COSTART  COUNT   61  RASH MAC PAP                 1
AGE      COUNT   61                               2
COSTART  COUNT   65  ANGIOEDEMA                   1
AGE      COUNT   65                               1
COSTART  COUNT   67  RASH VESIC BULL              1
AGE      COUNT   67                               1
COSTART  COUNT   69  ANGIOEDEMA                   1
COSTART  COUNT   69  PRURITUS                     1
COSTART  COUNT   69  RASH                         1
COSTART  COUNT   69  URTICARIA                    2
AGE      COUNT   69                               5
COSTART  COUNT   71  RASH                         1
AGE      COUNT   71                               1
COSTART  COUNT   72  RASH                         1
AGE      COUNT   72                               1
COSTART  COUNT   75  ERYTHEMA MULT                1
AGE      COUNT   75                               1
```

3[illegible] over age 55
24 over age 60
- over age 65

```
06/21/83                 CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION                  PAGE 108
                           CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

  PPA CONTAINING DRUGS

-----------------------------------------------------------------------------------------------------------
                 AGE          COSTART             TOTAL
                                               OCCURRENCES
-----------------------------------------------------------------------------------------------------------

  SKIN AND APPENDAGES

BODYCLAS COUNT                                     140

  SPECIAL SENSES

COSTART  COUNT          AMBLYOPIA                    2

COSTART  COUNT          CONJUNCTIVITIS               2

COSTART  COUNT          CORNEAL LESION               1

COSTART  COUNT          DEAF                         1

COSTART  COUNT          EYE DIS                      1

COSTART  COUNT          GLAUCOMA                     2

COSTART  COUNT          MYDRIASIS                    2

COSTART  COUNT          PAIN EAR                     2

COSTART  COUNT          PAIN EYE                     4

COSTART  COUNT          RETINAL DEGENERAT            1

COSTART  COUNT          TASTE PERVERS                1

COSTART  COUNT          TINNITUS                     1

COSTART  COUNT          VISION ABNORM                3

COSTART  COUNT          VISUAL FIELD DEFECT          1

AGE      COUNT                                      24

COSTART  COUNT      0   AMBLYOPIA                    1

AGE      COUNT      0                                1

COSTART  COUNT      3   PUPIL DIS                    1

AGE      COUNT      3                                1
```

```
---------------------------------------------------------------------------------------------------------------
                   AGE          COSTART            TOTAL
                                                 OCCURRENCES
---------------------------------------------------------------------------------------------------------------
  SPECIAL SENSES
COSTART  COUNT    4  MYDRIASIS                      1
AGE      COUNT    4                                 1
COSTART  COUNT   12  AMBLYOPIA                      1
COSTART  COUNT   12  CONJUNCTIVITIS                 2
COSTART  COUNT   12  MYDRIASIS                      2
COSTART  COUNT   12  PAIN EYE                       1
AGE      COUNT   12                                 6
COSTART  COUNT   17  ACCOMMODATION ABNORM           1
AGE      COUNT   17                                 1
COSTART  COUNT   18  CORNEAL LESION                 1
COSTART  COUNT   18  PAIN EYE                       1
AGE      COUNT   18                                 2
COSTART  COUNT   20  VISION ABNORM                  1
AGE      COUNT   20                                 1
COSTART  COUNT   21  CORNEAL LESION                 1
AGE      COUNT   21                                 1
COSTART  COUNT   23  CONJUNCTIVITIS                 1
AGE      COUNT   23                                 1
COSTART  COUNT   25  PHOTOPHOBIA                    2
AGE      COUNT   25                                 2
COSTART  COUNT   26  AMBLYOPIA                      1
AGE      COUNT   26                                 1
```

PPA CONTAINING DRUGS

		AGE	COSTART	TOTAL OCCURRENCES
SPECIAL SENSES				
COSTART	COUNT	27	CONJUNCTIVITIS	1
AGE	COUNT	27		1
COSTART	COUNT	28	DIPLOPIA	1
AGE	COUNT	28		1
COSTART	COUNT	30	AMBLYOPIA	1
AGE	COUNT	30		1
COSTART	COUNT	31	TASTE PERVERS	1
AGE	COUNT	31		1
COSTART	COUNT	32	CORNEAL LESION	2
COSTART	COUNT	32	PAIN EYE	1
COSTART	COUNT	32	VISION ABNORM	1
AGE	COUNT	32		4
COSTART	COUNT	35	VISION ABNORM	1
AGE	COUNT	35		1
COSTART	COUNT	37	VISION ABNORM	1
AGE	COUNT	37		1
COSTART	COUNT	38	CORNEAL LESION	1
AGE	COUNT	38		1
COSTART	COUNT	39	VESTIBUL DIS	1
AGE	COUNT	39		1
COSTART	COUNT	47	CORNEAL LESION	1

```
06/21/83                          CAUSE-EFFECT RELATIONSHIP BETWEEN EACH DRUG AND REACTION                PAGE 111
                                    CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES
  PPA CONTAINING DRUGS
---------------------------------------------------------------------------------------------------------------
                AGE            COSTART          TOTAL
                                             OCCURRENCES
---------------------------------------------------------------------------------------------------------------
  SPECIAL SENSES
AGE      COUNT   47                                 1
COSTART  COUNT   49  TINNITUS                       1
AGE      COUNT   49                                 1
COSTART  COUNT   54  TINNITUS                       1
AGE      COUNT   54                                 1
COSTART  COUNT   55  CORNEAL LESION                 1
AGE      COUNT   55                                 1
COSTART  COUNT   60  DEAF                           1
COSTART  COUNT   60  TINNITUS                       1
AGE      COUNT   60                                 2
COSTART  COUNT   71  AMBLYOPIA                      1
AGE      COUNT   71                                 1
COSTART  COUNT   72  CORNEAL LESION                 1
AGE      COUNT   72                                 1
BODYCLAS COUNT                                     62

  UROGENITAL SYSTEM
COSTART  COUNT       ALBUMINURIA                    1
COSTART  COUNT       BREAST ENLARGE                 2
COSTART  COUNT       DYSURIA                        2
COSTART  COUNT       GLYCOSURIA                     1
COSTART  COUNT       GYNECOMASTIA                   1
```

10 over age 55
8 over age 60
4 over age 65

```
  PPA CONTAINING DRUGS

-----------------------------------------------------------------------------------------------------------------
                 AGE          COSTART            TOTAL
                                               OCCURRENCES
-----------------------------------------------------------------------------------------------------------------

  UROGENITAL SYSTEM

COSTART  COUNT        HEMATURIA                      1
COSTART  COUNT        IMPOTENCE                      1
COSTART  COUNT        INFECT URIN TRACT              1
COSTART  COUNT        METRORRHAGIA                   2
COSTART  COUNT        PROSTAT DIS                    2
COSTART  COUNT        URIN IMPAIRED                  2
COSTART  COUNT        URIN RETENT                    9
AGE      COUNT                                      25
COSTART  COUNT     2  URIN ABNORM                    1
AGE      COUNT     2                                 1
COSTART  COUNT     3  HEMATURIA                      1
AGE      COUNT     3                                 1
COSTART  COUNT     4  POLYURIA                       1
AGE      COUNT     4                                 1
COSTART  COUNT    23  ALBUMINURIA                    1
COSTART  COUNT    23  URIN RETENT                    1
AGE      COUNT    23                                 2
COSTART  COUNT    26  AMENORRHEA                     1
AGE      COUNT    26                                 1
COSTART  COUNT    36  ABORTION                       1
AGE      COUNT    36                                 1
COSTART  COUNT    39  INCONTIN URIN                  2
```

312

```
 PPA CONTAINING DRUGS
--------------------------------------------------------------------------------------------
                AGE         COSTART        TOTAL
                                        OCCURRENCES
--------------------------------------------------------------------------------------------
 UROGENITAL SYSTEM

COSTART  COUNT   39  URIN RETENT               1
AGE      COUNT   39                            3
COSTART  COUNT   41  URIN RETENT               1
AGE      COUNT   41                            1
COSTART  COUNT   42  KIDNEY FUNC ABNORM        1
AGE      COUNT   42                            1
COSTART  COUNT   43  KIDNEY FAIL               1
AGE      COUNT   43                            1
COSTART  COUNT   52  URIN TRACT DIS            1
AGE      COUNT   52                            1
COSTART  COUNT   53  KIDNEY FAIL ACUTE         1
AGE      COUNT   53                            1
COSTART  COUNT   55  BREAST ENLARGE            1
COSTART  COUNT   55  URIN RETENT               1
AGE      COUNT   55                            2
COSTART  COUNT   56  BREAST ENLARGE            1
COSTART  COUNT   56  PAIN BREAST               1
AGE      COUNT   56                            2
COSTART  COUNT   57  URIN RETENT               1
AGE      COUNT   57                            1
COSTART  COUNT   58  KIDNEY FAIL               1
```

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```
  PPA CONTAINING DRUGS

------------------------------------------------------------------------------------------
                   AGE         COSTART          TOTAL
                                             OCCURRENCES
------------------------------------------------------------------------------------------

  UROGENITAL SYSTEM

 AGE      COUNT    58                               1
 COSTART  COUNT    62  URIN RETENT                  1
 AGE      COUNT    62                               1
 COSTART  COUNT    66  URIN RETENT                  1
 AGE      COUNT    66                               1
 COSTART  COUNT    70  URIN RETENT                  1
 AGE      COUNT    70                               1
 COSTART  COUNT    77  URIN RETENT                  1
 AGE      COUNT    77                               1
 COSTART  COUNT    81  URIN RETENT                  1
 AGE      COUNT    81                               1
 COSTART  COUNT    82  URIN RETENT                  1
 AGE      COUNT    82                               1
 COSTART  COUNT    89  INCONTIN URIN                2
 AGE      COUNT    89                               2
 BODYCLAS COUNT                                    54


 COSTART  COUNT        ANAPHYL                      1
 COSTART  COUNT        CONFUS                       1
 COSTART  COUNT        ECTROMELIA                   1
 COSTART  COUNT        NO DRUG EFFECT               1
```

23 over age 55
16 over age 60
14 over age 65

PPA CONTAINING DRUGS

```
                    AGE        COSTART              TOTAL
                                                 OCCURRENCES

AGE      COUNT                                        4
COSTART  COUNT       4   INSOMNIA                     1
AGE      COUNT       4                                1
COSTART  COUNT       6   PURPURA THROMBOPEN           1
AGE      COUNT       6                                1
COSTART  COUNT       7   PERSON DIS                   1
COSTART  COUNT       7   PURPURA THROMBOPEN           1
AGE      COUNT       7                                2
COSTART  COUNT      10   PURPURA THROMBOPEN           1
COSTART  COUNT      10   SOMNOLENCE                   1
AGE      COUNT      10                                2
COSTART  COUNT      13   EUPHORIA                     1
AGE      COUNT      13                                1
COSTART  COUNT      20   PSYCHOSIS                    1
AGE      COUNT      20                                1
COSTART  COUNT      21   CONFUS                       1
COSTART  COUNT      21   NERVOUSNESS                  1
AGE      COUNT      21                                2
COSTART  COUNT      27   ANXIETY                      1
AGE      COUNT      27                                1
COSTART  COUNT      28   CONFUS                       1
AGE      COUNT      28                                1
```

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```
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                              CANNOT BE ESTABLISHED WITH CERTAINTY IN ALL CASES

 PPA CONTAINING DRUGS

--------------------------------------------------------------------------------------------------------------
                  AGE        COSTART          TOTAL
                                           OCCURRENCES
--------------------------------------------------------------------------------------------------------------


COSTART  COUNT  29  DEPRESSION             1
COSTART  COUNT  29  INSOMNIA               1
AGE      COUNT  29                         2
COSTART  COUNT  31  OVERDOSE INTENT        1
AGE      COUNT  31                         1
COSTART  COUNT  38  ANXIETY                1
COSTART  COUNT  38  INSOMNIA               1
COSTART  COUNT  38  PSYCHOSIS              1
AGE      COUNT  38                         3
COSTART  COUNT  42  MELENA                 1
AGE      COUNT  42                         1
COSTART  COUNT  48  AMNESIA                1
COSTART  COUNT  48  INSOMNIA               1
AGE      COUNT  48                         2
COSTART  COUNT  69  PAIN INJECT SITE       1
AGE      COUNT  69                         1
BODYCLAS COUNT                            26
GENERIC  COUNT                          1040
```

2 over age 65

9

320

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VIRGINIA MASON
HOSPITAL

August 4, 1983

The honorable Mary Rose Oakar
House of Representatives
2436 Raburn Building
Washington D.C. 20515

Dear Congresswoman Oakar:

I am a member of the Washington State Board of Pharmacy. Our board for the past 18 months has been evaluating the non-prescription status of the OTC diet medications. I was made aware of your efforts in this area through media coverage of the recent House subcommittee hearings. I contacted Nancy LeaMond and had the opportunity to recently meet with Millie Vinicor. Both of these individuals requested that I forward to your attention background material dealing with our review of the OTC diet preparations. You will find enclosed board minutes, newspaper articles, and a copy of the statute giving the Board of Pharmacy authority to move drugs from non-prescription status to prescription status.

My interest in this area was initiated by an article in the Seattle Post Intelligencer (enclosed). As a result of that article I had the Board of Pharmacy staff invite to testify at an open hearing Dr. Michael Copass, director of the emergency trauma center at Harborview Medical Center here in Seattle. From that hearing and subsequent hearings I developed the opinion that not only were the look-alike drugs an issue that needed to be dealt with but also an evaluation of the non-prescription status of the over-the-counter diet aids.

As can be seen from the enclosed Board of Pharmacy minutes, a number of individuals representing differing points of view had the opportunity to present these points of view to the Board. Because of the volume of information and the differing points of view, I suggested the formation of an ad-hoc advisory committee to the board. The make-up of the committee includes physicians, pharmacologists, pharmacists as well as a physician representing the proprietary drug industry's interest.

Nancy LeaMond has been kind enough to put me in contact with Kirk Johnson, the assistant director of the National Clearing House on Diet-Pill Hazards at the Center for Science in the Public Interest. Mr. Johnson has forwarded me some of the material that they have developed relating to OTC diet medications.

The Board would appreciate any assistance that your staff may be able to provide

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Seattle, Washington 98111
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us in dealing with this issue. Likewise, if there is any more that we may be able to do in supporting your efforts in determining the need for national legislation related to these over-the-counter diet preparations, please do not hesitate to contact me.

Respectfully yours,

Arthur Zoloth

A. Zoloth, Pharm. D.
Director of Pharmacy
Member, Board of Pharmacy, State of Washington

AZ:11

cc: Board members

RCW 69.41.070 Penalties. Whoever violates any provision of this chapter shall, upon conviction, be fined and imprisoned as herein provided:

(1) For a violation of RCW 69.41.020, the offender shall be guilty of a felony.

(2) For a violation of RCW 69.41.030 involving the sale, delivery or possession with intent to sell or deliver, the offender shall be guilty of a felony.

(3) For a violation of RCW 69.41.030 involving possession, the offender shall be guilty of a misdemeanor.

(4) For a violation of RCW 69.41.040, the offender shall be guilty of a felony.

(5) For a violation of RCW 69.41.050, the offender shall be guilty of a misdemeanor.

(6) Any offense which is a violation of chapter 69.50 RCW shall not be charged under this chapter. [1973 1st ex.s. c 186 § 7.]

RCW 69.41.075 Rules——Availability of lists of drugs. The state board of pharmacy may make such rules for the enforcement and administration of this chapter as are deemed necessary or advisable. The board shall identify, by rule-making pursuant to chapter 34.04 RCW, those drugs which may be dispensed only on prescription or are restricted to use by practitioners, only. In so doing the board shall consider the toxicity or other potentiality for harmful effect of the drug, the method of its use, and any collateral safeguards necessary to its use. The board shall classify a drug as a legend drug where these considerations indicate the drug is not safe for use except under the supervision of a practitioner.

In identifying legend drugs the board may incorporate in its rules lists of drugs contained in commercial pharmaceutical publications by making specific reference to each such list and the date and edition of the commercial publication containing it. Any such lists so incorporated shall be available for public inspection at the headquarters of the state board of pharmacy and shall be available on request from the board upon payment of a reasonable fee to be set by the board. [1979 1st ex.s. c 139 § 3.]

SUBSTITUTION OF PRESCRIPTION DRUGS

RCW 69.41.100 Legislative recognition and declaration. The legislature recognizes the responsibility of the state to insure that the citizens of the state are offered the benefit of quality pharmaceutical products at competitive prices. Advances in the drug industry resulting from research and the elimination of counterfeiting of prescription drugs should benefit the users of the drugs. Pharmacy must continue to operate with accountability and effectiveness. The legislature hereby declares it to be the policy of the state that its citizens receive safe and therapeutically effective drug products at the most reasonable cost consistent with high drug quality standards. [1977 ex.s. c 352 § 1.]

Severability——1977 ex.s. c 352: "If any provision of this act, or its application to any person or circumstance is held invalid, the remainder of the act, or the application of the provision to other persons or circumstances is not affected." [1977 ex.s. c 352 § 10.] This applies to RCW 69.41.100–69.41.180.

RCW 69.41.110 Definitions. As used in RCW 69.41.100 through 69.41.180, the following words shall have the following meanings:

(1) "Brand name" means the proprietary or trade name selected by the manufacturer and placed upon a drug, its container, label, or wrapping at the time of packaging;

(2) "Generic name" means the official title of a drug or drug ingredients published in the latest edition of a nationally recognized pharmacopoeia or formulary;

(3) "Substitute" means to dispense, with the practitioner's authorization, a "therapeutically equivalent" drug product of the identical base or salt as the specific drug product prescribed: *Provided*, That with the practitioner's prior consent, therapeutically equivalent drugs other than the identical base or salt may be dispensed;

(4) "Therapeutically equivalent" means essentially the same efficacy and toxicity when administered to an individual in the same dosage regimen; and

(5) "Practitioner" means a physician, osteopathic physician and surgeon, dentist, veterinarian, or any other person authorized to prescribe drugs under the laws of this state. [1979 c 110 § 1; 1977 ex.s. c 352 § 2.]

RCW 69.41.120 Prescriptions to contain instruction as to whether or not a therapeutically equivalent generic drug may be substituted——Form——Contents——Procedure. Every drug prescription shall contain an instruction on whether or not a therapeutically equivalent generic drug may be substituted in its place, unless substitution is permitted under a prior-consent authorization.

If a written prescription is involved, the form shall have two signature lines at opposite ends on the bottom of the form. Under the line at the right side shall be clearly printed the words "DISPENSE AS WRITTEN". Under the line at the left side shall be clearly printed the words "SUBSTITUTION PERMITTED". The practitioner shall communicate the instructions to the pharmacist by signing the appropriate line. No prescription shall be valid without the signature of the practitioner on one of these lines.

If an oral prescription is involved, the practitioner or the practitioner's agent shall instruct the pharmacist as to whether or not a therapeutically equivalent generic drug may be substituted in its place. The pharmacist shall note the instructions on the file copy of the prescription.

The pharmacist shall note the manufacturer of the drug dispensed on the file copy of a written or oral prescription. [1979 c 110 § 2; 1977 ex.s. c 352 § 3.]

RCW 69.41.130 Savings in price to be passed on to purchaser. The pharmacist shall substitute an equivalent

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Seattle Post Intelligencer Sunday Nov 8, 1981

Three pills, then a stroke and paralysis

The state's 10th in tax burden

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PPA

· Subcommittee report (staff)
· Transcript of meeting

Seattle Times 7/22/83

Health hazards in diet pills told by scientists

Knight News Service

WASHINGTON — The principal ingredient in diet pills, on which Americans spend more than $220 million a year in usually fruitless attempts to lose weight, is not only ineffective but can also provoke strokes, cerebral hemorrhages and high blood pressure, a panel of scientists told a House subcommittee yesterday. — ?

The pills, sold as an appetite suppressant, are also taken by teen-agers seeking a legal "high", the scientists said, and are particularly dangerous to elderly persons who may unknowingly suffer from high blood pressure. One scientist said that the pills, when taken in combination with prescription drugs, can result in "an impossible toxicological situation."

The scientists, joined by four people who testified they had suffered severe reactions, including strokes, after taking pills made with phenylpropanolamine (PPA), called on the Food and Drug Administration to ban use of the drug in any kind of diet aid.

'They're ineffective. The risk is unacceptable and untenable.'

Dr. Thaddeus Prout

"They're ineffective. The risk is unacceptable and untenable," said Dr. Thaddeus Prout, a clinical pharmacologist at the Johns Hopkins University School of Medicine. "This is what I call the 'All-American Over The Counter Flim Flam' . . . .

"This is a fraud. It should be treated as a fraud and stopped."

The findings of the scientists were vigorously disputed, however, by a team of eight physicians and medical researchers sent to the hearing by Thompson Medical Co., a major manufacturer of PPA. They insisted their research showed that the drug is both safe and an effective way to lose weight.

However, even they conceded that patients taking PPA normally lose only about one pound a week — other patients given sugar pills lost a half-pound per week in the same studies — and had no explanation for the testimony of witnesses who said the drug caused them to suffer strokes.

"I believe we're hearing anecdotes here," said Dr. Matthew [illegible] of the Miami Heart Institute, who said an ongoing study of 34 patients with mild cases of high blood pressure shows that PPA has "no aggravating effects" on their hypertension. "It's coincidental. We've seen no evidence (that PPA causes strokes)."

But Gloria Jean Davis, a 33-year-old mother from Albany, Ga., who still wears a brace on her right leg, testified a diet-pill manufacturer paid her $125,000 to settle a lawsuit stemming from her 1978 stroke. Mrs. Anthea Saxe, a [illegible]-year-old Connecticut grandmother, said her doctor told her that the cerebral hemorrhage she suffered three years ago was caused by the diet pills she took to lose 10 pounds for her son's wedding.

And a Kentucky nurse said she checked herself into a hospital with abnormally high blood pressure and a low pulse rate after taking diet pills for just four days. Her doctor said she narrowly averted a stroke.

Even Rep. Geraldine Ferraro, D-N.Y. had her own anecdote, recalling the time she took diet pills to shed weight she had gained after quitting smoking. "I was amazed," she said. "After three days, my heart beat very fast. I cleaned my house like a white tornado . . . I was a nervous wreck."

"They (the FDA) know they are remiss," charged Rep. Mary Rose Oakar, D-Ohio, who announced she was introducing a bill that would seek to identify and remove hazardous drugs from the market.

FDA Commissioner Arthur Hayes Jr. was invited to testify, but a spokesman said a scheduling conflict prevented him from doing so.

In a written statement presented to the panel later in the day, the FDA did not directly respond to the charges of [illegible], but cited ongoing studies of the safety and effectiveness of all over-the-counter drugs.

THE FOUR HUNDRED AND THIRTY-SIXTH
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

December 3 and 4, 1981

The four hundred and thirty-sixth meeting of the Washington State Board of Pharmacy was called to order at 9:10 a.m. by Chairman Arthur Zoloth in the conference room of the King County Precinct 4, 14905 Sixth Avenue SW, Burien, Washington, on Thursday, December 3, 1981. Present were Chairman Zoloth; Vice-Chairman Lars Hennum; Board Members Harold F. Osborne, David H. Palmer, and Edyrn H. Jones; Executive Secretary Donald H. Williams; Chief Investigator Charles James; Barbara Phillips, AAG; and Mary-Helen Hansen, clerk.

Mr. John Welsh, Counsel, speaking on behalf of Chairman James Mitchell of the House Human Services Committee, presented and discussed a proposed amendment to the Controlled Substances Act which would prohibit the sale of imitation controlled substances ("look-alikes"). The amendment is based on a Model Act developed by the Drug Enforcement Administration for consideration by individual states. Presently sixteen states now have some legislation in this area. The proposed legislation would outlaw the manufacture, distribution, and possession of "look-alikes", or imitative controlled substances, and plug a loophole in the present law. The present law makes it a crime to sell a fake controlled substance fraudulently. This Bill addresses the question of attempting to sell or selling something that looks like a controlled substance without representing it to be a controlled substance. The intent of the seller is to pass the drug off to the buyer as a controlled substance for resale, so that the buyer ends up making an inordinate profit, representing the drugs not directly as controlled substances. These drugs have been made to look like controlled substances and made in concentrated quantities of caffeine, ephedrine, phenylpropanolamine, and other substances that may cause injury or even death to users. The market is largely youth - from adolescence through college. The advertising is open and nonsecretive. Purchases can be made by mail or at truck stops, "head shops", and other places. These drugs are illegal in Washington if they contain ephedrine.

Chairman Zoloth asked Mrs. Phillips if the Board had the authority under RCW 18.64 to promulgate regulations on "look-alikes". She replied that criminal penalties could not be created by regulation, and that while the Board may or may not have the authority, statute would provide the stronger penalties needed.

The Bill defines "imitation controlled substances" and addresses intent to deceive by the seller. Also it creates crimes, prohibits advertising, lists exemptions from liability of the Bill, contains provisions for seizure and forfeiture, and adds a new chapter to Section 69 RCW. No problem is anticipated in passing the Bill.

Board members: suggested that the amount of tablets in possession be considered as intent to sell: expressed concern about legitimate OTC products now in the pharmacy; and questioned the possible abuse of phenylpropanolamine (PPA) and the need for Board action in this area. Mr. Welsh suggested that the Board hold a public hearing on PPA abuse with input from concerned parents and school personnel.

Mr. Hennum moved that the Board draft a resolution in support of the proposed legislation dealing with imitation controlled substances, and that the individual Board members - as they personally feel - may submit individual statements as well. Motion passed.

Mr. Hennum moved to send a letter to the legislature that they consider removing the laetrile statute as there have been no applications for manufacture since enactment. Motion passed.

The Board discussed the advisability of requesting the legislature to place all DMSO on prescription status as recommended by the DMSO Task Force and determined that a letter should be sent to the Joint Administrative Rules Review Committee recommending that all DMSO sold at retail must meet the purity standards set forth by the Board.

Board members discussed abuse of PPA products and requested that the Board office contact manufacturers, NIDA, Board inspectors, the State Medical Association, a pharmacologist, and poison control centers, as well as concerned organizations of parents, and inform them the Board is considering making PPA a legend drug and will hold a public hearing in the near future.

Mr. Duc Nguyen of Saigon Drug, wholesaler, appeared before the Board to discuss his proposed operation of packaging and exporting legend drugs to Vietnam. The Board had deferred action on his application (October meeting) for a wholesaler license. Packaged legend drugs purchased by his customers are sent by him directly to private individuals in Vietnam via Air France or the U.S. Postal Service.

Mr. Osborne moved to grant the wholesale license. Motion passed.

The Board reviewed Oregon's wholesale law export section as a possible model for a Board regulation for wholesalers.

Mr. Palmer moved to draft wholesaler regulations using the Oregon law with appropriate changes for Washington regulations. Motion passed.

Mr. Hennum moved that both Mekong Pharma Inc. and Saigon Drug - wholesalers - start keeping records along the line of what will be a proposed regulation so that at the time of the regulation hearing, they can give input as to the accuracy of records, and start keeping records in the correct manner - and that this be so stated by letter. Motion passed.

Mr. Jones asked that the Board staff assist the two exporters in setting up record keeping procedures.

Mrs. Phillips advised that she will file these regulations for a formal hearing in February.

Mr. Nghia Doan explained the operations of Mekong Pharma Inc. Both wholesalers were thanked for appearing and explaining the procedures and for their assistance to the Board.

THE FOUR HUNDRED AND THIRTY-EIGHTH
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

February 18 and 19, 1982

The four hundred and thirty-eighth meeting of the Washington State Board of Pharmacy was called to order at 9:18 a.m. on Thursday, February 18, 1982, by Chairman Dr. Arthur Zoloth in the conference room of King County Precinct 4, 14905 Sixth Avenue SW, Burien WA. Board members present were Chairman Zoloth, Vice-Chairman Lars Hennum, Harold F. Osborne, and David H. Palmer. Board Member Edyrn H. Jones was excused for illness. Board staff members were: Donald H. Williams, Executive Secretary, Chief Compliance Investigator Charles James, AAG Barbara Phillips, and Mary-Helen Hansen, clerk.

Chairman Zoloth opened a discussion of the abuse potential of cough syrups containing codeine and the dangers of Phenylpropanolamine (PPA). Dr. Zoloth introduced Dr. Lawrence Halpern, Department of Pharmacology, University of Washington Health Sciences. Dr. Halpern had been invited by the Board to discuss the appropriate use of codeine in Schedule V cough syrups and phenylpropanolamine as a drug in diet aids and "look alike" tablets.

Dr. Halpern felt the Board should consider:

1) After two or three weeks, people are buying the cough syrup for other than cough suppression.

2) Does the volume amount in a 4 oz. bottle of cough syrup fit the time covered for use?

3) Codeine vs. dextromothorphan: dextromothorphan is not as effective as a cough suppressant - not as good a centrally acting drug as it is an anti-tussive.

4) The tie-in with alcohol in the cough syrup is the attraction for abusers.

5) Is the practice of selling the cough syrups by the pharmacies contributing to drug abuse? Good pharmacy practice? Good medical practice?

6) Home dosage; patients increase dosage. A drug should be taken according to instructions. If it does not work, the patient should check back with the physician for other medications.

7) Prescription only? Check with chest physician for prescription or non-prescription information. It may not be needed for long term use. Perhaps the MD is restricting prescriptions.

8) Ineffective home remedies. The cost benefit - the charge for prescriptions by the physician and the pharmacy.

In summary, Dr. Halpern suggested the Board seek guidance from a pediatrician and a chest physician concerning amounts of codeine cough syrups to be prescribed.

According to Dr. Halpern, phenylpropanolamine was a third generation diet pill, a decongestant with the same potential for adverse action as amphetamines: Paranoid toxicity due to increased dosage, plus deep, long-lasting depression. It was not approved by the Food and Drug Administration, but by a panel appointed by the FDA who approved it for weight control. With "look alikes" the danger to users was overdosing on real "speed". PPA was a useless kind of medication that was not effective in weight loss over a long period of time. The patient was treating depression rather than the weight problem.

Dr. Michael Copass MD, Harborview Hospital, Seattle WA, stated that very few people need a chronic cough syrup, possibly only those with smoker's cough. Self medication has become a national habit. The abuse potential for Schedule V cough syrups is moderately high. Pharmacies selling most of the Schedule V cough syrups may be located in an area where much drug abuse occurs. 48 hours between sales to an individual may be too short. He suggested the Board should find out what the pharmacists are saying to the patients about its use. The pharmacist may need more control over the frequency of allocation. He felt that codeine was not needed. In the matter of phenylpropanolamine Dr. Copass related some statistics: Although Ritalin was still the largest drug of abuse in Seattle in 1981, Benzedrine was second. In July 1981, there were two emergency PPA cases at Harborview Hospital, in December 1981, there were 50. In the middle age group, it was diet aid PPA's, among teenagers, it was "look alike" PPA's. He felt that this was just a beginning. Dr. Copass discussed the effects of PPA - hypertensive hemorrhage due to malignant hypertension, a tremendous "buzz", severe agitation, and - after treatment - a deep depression. He stated that "look alikes" needed to be looked at by both the pharmacy and the medical professions, because it needed to be stopped. "By allowing the medicines, we are generating a patient population", he said. Two to three mg's per day were all right as a decongestant; 65 to 85mg's could be tolerated as a diet aid; but 85 to 200 or 300mg's per day resulted in very high blood pressure. The attraction is in the "head set" or mental effect that this so-called "speed" produces. Dr. Copass agreed that both cough syrups and PPA products were in question as to clinical effectiveness and may add to the drug abuse problem in the community.

Mr. Norman Johnson of Therapeutic Health Services, a drug abuse program in Seattle, discussed the use of cough syrups among the clients he is treating in his clinic. Most of them condemn the use, but most use it to tide them over and prevent withdrawal symptoms. He stated that he was not aware that the use was so wide spread. He was very upset at the ease with which it was obtained. The drug users were now getting alcohol in addition to the codeine. He is very concerned that the 60 day stabilizing period for his clients is being offset by the cough syrups that they can get very easily. He felt that pharmacists should be given some controls over the dispensing of cough syrups. He questioned the amount and frequency of availability of the medication, and the prolonged sales to users. He had not seen any PPA use to date. He introduced Debbie Fisher, a client in his program for pregnant addicts. Mrs. Fisher discussed her knowledge of the easy availability of codeine cough syrups and amount of money and effort spent by users to obtain a supply. Four and five bottles per day was an average use; $500 to $700 per month was spent on bottles of cough syrup. She described the

THE FOUR HUNDRED AND THIRTY-NINTH
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

March 18 and 19, 1982

The four hundred and thirty-ninth meeting of the Washington State Board of Pharmacy was called to order at 9:05 a.m. on Thursday, March 18, 1982, by Chairman Dr. Arthur Zoloth in the conference room of King County Precinct 4, 14905 6th Avenue SW, Burien, Washington. Present were Chairman Zoloth; Vice-Chairman Lars Hennum; Board Members Harold F. Osborne and David H. Palmer; Executive Secretary Donald H. Williams; Assistant Attorney General Barbara Phillips, and Mary-Helen Hansen, clerk. Also present were Chief Investigators David Campbell and Charles James, and Board Investigators Willard Scott, Frank Bracelin, Hobart Ashmore, Bob Miller, and Dick Morrison.

Chairman Zoloth announced that the formal regulation hearing scheduled for 9:00 a.m. to repeal WAC 360-16-110, the old Hospital Pharmacy regulations inadvertently left in effect when chapter 360-17 WAC was adopted, would not be heard because of a problem with notices. The hearing will be continued to the April meeting.

The Board then met in a Closed Meeting with the Investigators.

At 10:25 a.m. the Open Meeting was resumed. Chairman Zoloth announced that the Board of Pharmacy had the authority to determine which drugs were legend drugs, and the Board was considering making Phenylpropanolamine a legend drug. The Board had asked representatives from industry and medicine to present information on Phenylpropanolamine (PPA) for a proposed regulation hearing.

Dr. Edward Steinberg, Ph.D., Vice-Chairman
Thompson Medical Company
New York NY

Dr. Steinberg stated that the Food & Drug Administration miscellaneous internal review panel of physicians (report published February 1982) recommended Phenylpropanolamine as safe and effective for appetite suppression for weight control for a period of use of 12 weeks when used as directed. PPA has been used for 40 years as an appetite suppressant. An estimated 10 million people currently take a weight loss product. It is a proven aid to weight loss with no significant changes in blood pressure, pulse rate, or side effects. The FDA panel conclusion was based on clinical and laboratory studies submitted by Thompson Medical Company and others. The studies were based on hundreds of patients with thousands of patient days under medical supervision. There are no new statistics to indicate it is unsafe. The legal dosage in the United States is 25mg three times per day, or 75mg total once a day in a time release capsule. Dr. Steinberg believed PPA to be without tolerance or abuse potential. In Australia, according to an article in The Lancet (1980), an 85mg immediate release form caused some elevation in blood pressure.

In tests with animals - rats and monkeys - PPA reduced food intake with a lack of hyperactivity and stimulatory effect. Human studies show that the weight loss from use of PPA was at least equal to the weight loss by any prescription drug, with none of the attendant side effects, and twice as effective as a placebo under clinical conditions. This product is important to millions of consumers who are motivated to take off weight and need such a modality. He felt that young people who may be trying PPA for purposes of achieving a "high" will be disappointed. A check with all related federal agencies, plus checking with researchers who had conducted studies with 18,000 teenagers (federally financed study of drug use with numbers of drugs) showed no PPA abuse. PPA was not listed separately by Poison Control Centers of DAWN (Drug Abuse Warning Network). The data listing 10, 000 poison control cases with 1000 Emergency Room incidents involving PPA weight control products occurring each year is not true (Vol. 25, August 1981, Bulletin National Clearinghouse for Poison Control Centers). The figure is an estimate, according to the senior author of the report. 739 was the actual number. None of the 10,000 cases has been checked out. He felt that the statistics were picking up the use of street drug "look alikes".

Caffeine is included in diet aids to offset lethargy caused when an individual goes on a reduced caloric intake. His company produces products both with and without caffeine. Dosage of PPA permitted by the FDA for diet aids is 75mg per day; for the cough and cold industry, it is 150mg per day. Studies indicate there is no problem with higher doses - 150mg - in a 24 hour period.

Dr. Steinberg stated that the illegal drug "look alike" problem was a matter requiring appropriate federal and state scrutiny and general improvement of safety precautions in the home. Thompson Medical's packaging and labeling precautions were effective and responsible and should not be penalized because others are making "look alikes". He quoted the consumer member "watchdog" of the FDA panel, Michael Shulman of USC, as saying he was impressed with the evidence and in his judgment PPA was safe, effective, and in the best interests of the public. 12 weeks were established as a time frame by the FDA because Thompson Medical had submitted studies up to 12 weeks. His company is updating data on longer term use. There are no states that currently require prescription for these products. Thompson is an OTC company with no prescription products and would penalized by a vast reduction in sales.

Dr. Steinberg introduced Ms. Sunny Wilson, Cosmopolis, Washington, who talked about her use of PPA. She lost 76 pounds in 12 weeks with the use of a Thompson product. She had tried other diets without success. She has maintained her achieved weight for over six months. She takes one capsule per week or as needed.

Dr. Harold I. Silverman, Ph.D., RPh.
Professor of Pharmacy
Executive Director, Pfifer Research Laboratory
Massachusetts College of Pharmacy
Member of Faculty, Boston University School of Medicine
Consultant to Thompson Medical Company

Dr. Silverman stated that problems, if there were any, were not due to the legitimate use of Phenylpropanolamine. Used appropriately in correct dose, the drug was safe and effective. His original research found the drug to be efficacious and not to produce any adverse effects when used appropriately. He cited a report from the National Clearinghouse for Poison Control Centers, reporting incidents from all drugs - 65-66,000 incidents - that there were no reported deaths from PPA, though there were many from other drugs. He felt PPA was incapable of being abused and incapable of being used in a way which would cause either euphoria or stimulation. It was an effective nasal decongestant and effective anorexient. He felt that because it falls within the category of Central Nervous System stimulants, that it is assumed that PPA will have a stimulant effect.

Dr. Silverman felt that "look alikes" were the problem. With regard to caffeine and PPA, DEA felt that more deaths from caffeine overdoses may have gone unreported. There were no deaths from PPA. Thompson studies had not shown a synergistic effect for PPA and caffeine together. PPA did give a feeling of disphoria, but no euphoria. In independent studies at Johns Hopkins University, involving primates, higher doses had shown no drug abuse or bizarre behavior. There were no published human studies. Overdosing with PPA, caffeine, or a host of other substances will increase blood pressure. There were no problems in studies as submitted to the FDA where 75mg to 150mg per day were used.

Dr. Silverman discussed the study done by Horowitz in Australia on a product not available in the United States. It was not the same as the U. S. PPA. There were four different isomers of PPA. DL racemic was the form used in this country. In Australia, it was D PPA, the dextro form, 85mg, immediate release. He had not received enough tablets to test for increase in blood pressure. This product was no longer on the market in Australia. The study was only to be used as a guide. He was not aware of hypertensive incidents in this country the same as Horowitz reported in Australia. There were no deliberate studies being developed with humans with regard to high blood pressure or toxicity because of the risk. He was not aware of adverse effects in either the blood forming organs or the cardio-vascular systems. A lot of PPA has been given, but the studies only run for about three months at a time. Statistics have only been developed over the last 12-15 months. Thompson Medical is mapping out what it will do next with data for long term use.

John Grunzell MD
Professor of Medicine
Department of Medicine
Division of Metabolism and Endocrinology
University of Washington
Seattle, Washington

Dr. Grunzell explained that he was interested in the metabolism of obesity and would discuss the problem from the viewpoint of the physician. Obesity was both a health problem and a sociological problem. The health related problems were problems with blood sugar/diabetes; high blood fat levels/triglycerates or chloresterol; and elevated blood pressure. All of the risks for obesity for heart disease and strokes seem to be mediated through one of these three diseases. He stated that it has been demonstrated that weight loss would ameliorate all of these abnormalities, so there was a need to find a system so that people could take off weight and keep it off. There were many ways to lose weight, including diets, behavior modification, and drugs. Weight loss was not the problem. Maintenance of weight loss after the desired weight was lost was the problem. Today, there was no way to take off weight and keep it off, if you followed the patients over a number of years. Two percent of the population could take off weight and keep it off for nine years. There was very little data other than short term follow-up on maintenance of weight loss to indicate that drugs are efficacious or not efficacious. Drugs available include adrenalin-like; amphetamine-like (Fenfluoramine and PPA may be a separate subclass); thyroid-like, no longer used; and other drugs which block the absorption of certain kinds of foods. Amphetamines and PPA are anorexic and dry up secretions, which is the reason for the use of PPA in cough syrups. Most have a Central Nervous System effect. Many help in weight loss. There is not much evidence to suggest that PPA does much more to help weight loss than the desire to lose weight alone.

Dr. Grunzell quoted from Thompson Medical Company's own contraindications as published in the Physician's Desk Reference for the 75mg tablet:

> "Do not exceed recommended dose. If nervousness, dizziness, sleepiness, rapid pulse, palpitation, or other symptoms occur, discontinue medication and consult your physician. If you have or are being treated for high blood pressure, heart, diabetes, thyroid, or other diseases, while pregnant, or nursing under the age of 18, do not take this drug except under the advice of a physician."

He identified those people who are overweight or who have obesity associated with a health problem, other than the massively obese individual, as people at risk for stroke, for heart attacks. related to diabetes, high blood fat levels, and high blood pressure. For these people, he felt the drug was contraindicated, according to Thompson Medical Company.

In summary: 1) He was not sure there was a successful way short of surgery for keeping weight off once the person had lost the weight. 2) If there was a way to take weight off and keep it off, there was no data on long-term weight maintenance, using any of these medications compared to simple caloric restrictions. There was no evidence of efficacy. 3) If a study is done, he feels there is no reason to accept PPA over Fenfluoramine, or some other drugs. Finally, if these PPA drugs are important and individuals who need these medications are identified, Dr. Grunzell felt they should be regulated by a physician who could look for the risk factors and take care of the potential problems.

Dr. Stephen Woods, Ph.D.
Professor and Chairman, Department of Psychology
Department of Medicine
University of Washington
Seattle, Washington

Dr. Woods commented on PPA. There were no published long-term studies on the efficacy of PPA. There is a high tendency to regain weight. He quoted weight loss studies at Princeton: People who received a placebo lost 1½ pounds over a 10-12 week period, while those who got PPA lost 2½ pounds over the same period. (NOTE: We believe Dr. Woods meant to add "per week" to the pound figure quoted.) The combined effect was greater than PPA itself. He felt that it was significantly higher than the placebo effect or the desire to lose weight. He felt the evidence was in favor of the concept that PPA does act by getting into the Central Nervous System, the sited action is in the same part of the brain that stimulation occurs. There is a big void in the literature. Many drugs are not being tested by psychologists with regard to the ability to reduce appetite and to take off weight. A series of control experiments need to be done to show that these drugs are acting in some natural way on the appetite systems. There are no studies on PPA. Does PPA cause an aversion response - taste aversion? In common testing, the drug is given to animals to see if when they stop eating they undergo the same behaviors that they undergo after a normal meal, but that this is happening sooner in time with the drug. The test is called complete behaviorial satiety. This has not been done with PPA, though it has been done with other drugs in that family, and all cause very large disruptions of normal behavior. Finally, a critical study would be the degree of weight loss over a period of time and the ability to keep the weight off, given the prescribed regimen. He felt the Board needs to weigh the potential for beginning to lose weight and maintaining that regimen for a period of time - in addition, the number of people who are seeking to lose weight without consulting a physician - against the real efficacy of Phenylpropanolamine and a possible potential for abuse.

Mark J. Ugoretz
Assistant General Counsel
The Proprietary Association
Washington, D. C.

Mr. Ugoretz identified The Proprietary Association as a one hundred year old trade association representing manufacturers of non-prescription medicine whose products are marketed throughout Washington. He stated that he had been working on the issue of street drug "look alikes" for about two years. He referred to the FDA panel report that PPA was safe and effective as a diet aid and did not require supervision for use. PPA seems to be connected with the abuse of drugs in unapproved combinations such as caffeine, ephedrine, doxylamine, and other ingredients. These are misbranded and have no NDA. He distributed documents to the Board that reviewed the laws with regard to "look alikes" and gave background information on the issue. 43 states are looking at this problem which does not include legitimate OTC drugs sold in retail outlets. PPA appears to be used to permit the drugs to masquerade as legitimate products. 17 states have passed laws; 26 are still considering it. (NOTE: Washington legislation was attached to another House Bill than 815 and passed.) In states that have passed bills based on the DEA Model legislation or the AMA bill, the distribution and abuse of street drug "look alikes" has declined. Not one of the 43 states has restricted PPA to prescription or anyway prevented consumers from obtaining diet aid products. In his travels through other states, he has discussed PPA and other states do not appear to have the problem. The problem of PPA showing up in reports will be resolved when the "look alikes" are outlawed. He asked the Board to provide his Association the opportunity to examine data, the specific number of actual instances with legitimate OTC products containing PPA that were purchased for improper use, where purchased, and by whom. (He was told that the Board's responsibility was to the public, and that if the Board found sufficient reason to act, it would.) He was not aware of the problem in other states. He warned that Washington consumers will suffer the inconvenience of loss of outlets if PPA is put on prescription status. There will be price increases and the need for doctors' visits and the prescription prices added - if the product can be found. OTC products will be purchased out-of-state. The products will be misbranded, unless the pharmacist attaches a state legend label. He urged the Board to await passage of legislation regarding "look alikes". In summary, PPA was a safe and effective drug. In other states which had considered legislation, abuse was found to be in conjunction with other drugs and fraudulently sold as street "look alikes".

Dr. Raymond Ragland Ph.D.
Menley & James Laboratories
Division of Smith Kline & French
Philadelphia PA

Dr. Ragland stated that his company had been in contact with poison control centers and their data was inconsistent with what the Washington Board of Pharmacy's data suggests.

Dr. Evan G. Siegal
Scientific Affairs Associate
The Proprietary Association
Washington, D.C.

Dr. Siegal explained that his background was in molecular biology, pharmacology, and toxicology, as well as medical genetics at two universities and the FDA. He reviews literature and reports - information from federal agencies and poison control centers, published and unpublished literature, reports from consumer groups, and mortality and morbidity reports from the Center for Disease Control in Atlanta. He was a PTA president of his son's school and alternate delegate to the county Board of Education in Maryland. Any information regarding drug abuse would come to him. He suggested that althougth PPA resembled an amphetamine-like compound, it actually may prevent some of the stimulation that is known to be caused by amphetamines. PPA is known to be excreted by humans at a rate of 97% unchanged in the urine in 24 hours. A receptor binding and blocking action may eventually be proved to occur. The "olamine" at the end of PPA can - to the uneducated mind - be likened to amphetamine controlled substances. The kids may be linking "look alikes" to PPA and grabbing diet aids to get a supposed "high". He has no data to show, but he feels it is human nature to look for other sources when one particular source is not available. He cited the unstable psychological state of teenagers - they would take anything and continue to use without effect. The supposed effect may be psychological response. He quoted from the 1981 report of Poison Control Centers: "No irferences should be drawn from the data concerning the true incidents of poisoning signs and symptoms, hospitalization, death, or other aspects of the problem". The reports are basically anecdotal and may have nothing to do with adverse effects - cause and effect - of PPA. According to DAWN, the peak of the PPA cases were teenagers 14-18 years of age. There was nothing after the age of 18 in incidents of PPA related effects. There are 10 million dieters who are in the adult age population. In the latest data to December 1981 from Emergency Room visits, PPA related incidents had dropped two-thirds in the last half of 1981. He suggested that the Board may have part of the answer nationwide to the increase of Emergency Room visits due to PPA. There are very few analyses of what drugs were present in reports, they are mostly anecdotal.

All speakers were thanked for their contributions and time. Mr. Williams requested the source of the 739 PPA incident figure reported by Drs. Steinberg and Silverman.

Chairman Zoloth reconvened the afternoon session at 2:30 p.m.

Steve Smith, Assistant Attorney General, presented the following Order:

Jimmie Alan Tibbets RPh.
Clallam Bay WA

Possession of legend drugs without prescriptions or orders, possession of controlled substances without prescriptions or orders.

Final Order on Stipulated Settlement: License suspended for 5 years, 4 years stayed, unless further violations of any state or federal law, rule or regulation relating to the practice of pharmacy during a 5-year period, beginning with the date of this Order. Prior to reinstatement:

1) Participate in drug abuse program approved by the Board and provide evidence of such participation.

2) Documentation by two professional therapists that it would be appropriate to reinstate license.

3) Take and pass the law exam.

THE FOUR HUNDRED AND FORTY-SECOND
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

June 24 and 25, 1982

The four hundred and forty-second meeting of the Washington State Board of Pharmacy was called to order by Chairman Lars Hennum at 9:13 a.m. on Thursday, June 24, 1982, in the conference room of King County Precinct 4, 14905 6th Avenue SW, Burien, Washington. Those present were Chairman Hennum; Vice-Chairman Harold F. Osborne; Board members David H. Palmer, Joseph J. Thompson, and Dr. Arthur Zoloth; Executive Secretary Donald H. Williams; Assistant Attorney General Barbara Phillips; and Mary-Helen Hansen, Clerk.

The meeting opened with a presentation "Look Alike Drug Research and Physician Training Project and Diet Aid Misuse and Abuse" by Drs. Donald R. Wesson MD and John P. Morgan MD of the Drug Look Alike Research and Training Project, 409 Clayton Street, San Francisco CA 94117, associated with the Haight-Ashbury Free Clinic in San Francisco. Dr. Wesson, a psychiatrist, illustrated his report with slides which showed look-alikes, drugs of deception, stimulants, diet pills, and cocaine look-alikes. Since amphetamines have been traditionally the drugs of abuse, fake "speed" is manufactured to closely resemble legitimate amphetamine tablets in form and marking, as well as containing chemicals known to produce a similar mood effect: e.g., caffeine, ephedrine, and phenylpropanolamine. The danger to youthful drug users is in their consuming a large, multi-unit dose. Dr. Wesson stated that his research has failed to turn up information on medical or psychiatric complications from escalated dosages of OTC diet pills by chronic users. "Look-alikes" are not viewed as potent and are unlikely to be used alone in suicide attempts.

Dr. Morgan, is Medical Professor and Director at the Pharmacology Program, Sophie Davis School of Biomedical Education, City College of New York. His presentation began with a history of the amphetamine popularity of the sixties which resulted in the advent of look alikes when the DEA action to place amphetaminesin Schedule II of the Controlled Substances Act successfully curtailed manufacture of amphetamines. The triple combination of caffeine, ephedrine, and phenylpropanolamine has made up the bulk of stimulant sales, and nearly all deceptive products contain this combination. According to Dr. Morgan, no legitimate OTC preparation is manufactured in this triple combination. Manufacture and mail order sales of look-alike pills became evident in the late seventies and are now widespread. Ads are directed toward bulk purchases and resale is encouraged. The initial reaction by our culture is to respond with anger, fear, concern, and to formulate laws. Dr. Morgan felt that evidence that these drugs are dangerous is unconvincing. Caffeine is used daily by millions, and ephedrine and PPA are used successfully as bronchodilator and decongestant. Dr. Morgan suggested that states should wait to see what the Federal government initiated with regard to curtaining look alikes. The Federal government has already shut down several illegal manufactures, as counterfeit drugs are adulterated and mislabeled. The Post Office has enjoined mail order advertising at this point. Self medication is part of appropriate health care and should not impaired by restricting access to these agents such as OTC caffeine, ephedrine and PPA. Dr. Morgan admitted that PPA is hypertensive, but stated that he did not know what effect massive doses would have on the user. He had heard of several reported deaths from overdoses of look-alikes, but the medical evidence was not complete. In response to questions from Board members, concerned that the evidence presented was contrary to presentations from University of Washington physicians and professors, Dr. Morgan confirmed that money for their research comes in part from manufacturers and members of the The Proprietary Association. However, he felt the Board's concern and interest in prescription only status was valid, and he doubted that the caffeine/PPA diet aids were significantly therapeutic in the long run. He did not wish to see over-regulation of drugs for "people's own good" while responsibility for one's own health was now becoming the mode in American life.

Requests for exemption from the imprint law deadline were considered by the Board:

Abbot Laboratories - Paradione
*Continue to next meeting.

Upjohn - request for further extension of time. Mr. Rogers of Upjohn was present at the meeting.
*The Board voted to grant extension to January 1, 1983, for the following products contingent upon receipt of a letter of intent to comply from Upjohn:

Maolate 400mg, Fominone 0.05mg, Pamine Bromide 2.5mg, Cortef 5/10/20mg, Didrex 50mg, Provera 2.5mg, Delta Albaplex, Albaplex, Lincocin 100/200/500mg(Veterinary), Cortabs(Veterinary), Panmycin Hydrochloride Bolus Veterinary, Medrol 1mg(Vet).

Endo Laboratories - Tessalon Perles will be imprinted per letter of 6-22-82 requesting extension to October 1, 1982.
*Board approved extension to October 1, 1982 - then unimprinted products must be recalled from wholesalers in the state.

Dura Pharmaceuticals - Dura-Vent, Dura-Vent/A, and Dura-Vent/DA all will be imprinted by August 30, 1982. Mr. Wheeler and Mr. Evangelisti were present to request extention.
*Board granted extension contingent upon letter of intent.

Winthrop Laboratories have notified the Board by letter that Luminal Ovoids will no longer be manufactured.

Dr. Zoloth requested that regulations be developed that would require manufacturers to update information and present it in standardized format.

It was moved, seconded, and passed that the request of Albert E. DelPalacio, Jr. for a waiver of a portion of his intern hours requirement be granted.

The following Pharmacy Assistant training programs presented by Mr. Palmer were approved by the Board:

THE FOUR HUNDRED AND FORTY-FIFTH
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

September 16 and 17, 1982

Burien Police Department
14905 6th Avenue SW
Burien WA

9:10 a.m.

Present:	Board Members
Lars Hennum	Chairman
Harold H. Osborne	Vice Chairman
Joseph J. Thompson	
David H. Palmer	
Dr. Arthur Zoloth	
Donald H. Williams	Executive Secretary
Joyce Roper	Assistant Attorney General
Mary-Helen Hansen	Clerk

The Board discussed a letter written by Assistant Attorney General Barbara Phillips to Dr. Edward J. Hannity DPM concerning statute RCW 69.41.120 which required all written prescriptions to contain two signature lines. Dr. Zoloth suggested that the Board review generic substitution prescription blanks - that this portion of the law be reviewed to allow doctors to add own method of choice of the drug to be dispensed. Mr. Williams was asked to ask the Medical Association for input regarding the generic substitution lines for possible revision during the present legislative session, with a copy of the letter to the physicians that have complained to the Board.

It was moved, seconded, and passed that the following requests be granted:

-- Lisa A. Speigelberg, Bellevue WA - Internship credit for special project with the Health Care Financing Administration, Mike Kopcho RPh, Supervisor.

-- Ann Donnelly, Anaheim Hills CA - request for licensure by taking the law exam, approval of experience as a pharmacist in Canada. Ms. Donnelly graduated from the University of Washington in 1958 and completed the written portion of the Full Board examinations and 674 hours of Internship. She is licensed in California.

The Board determined that patient profiles records were a part of the prescription records and should be retained by pharmacies for five years. If these are purged from the computer they should be placed on microfiche (RCW 18.64.245). Board intent is to be clarified in regulation WAC 360-16-260, and the time period is to be included. The information should be published in the January Newsletter.

Chairman Hennum requested that the status of pharmacy and pharmacist licenses after the renewal date be made an agenda item in October and in November for licensee input. Mrs. Phillips has stated that the grace period as stated in statute refers only to the submission of the renewal fee without penalty, and not to a grace period for license expiration. This will also be published in the January Newsletter. The regulation should appear under licenses and fees WAC 360-18 to clarify the interpretation.

The Board discussed hospital pharmacy licensing where multiple sites were involved. Presently, inpatient and outpatient pharmacies must have separate licenses when not in the same location. It was suggested that a master license for a hospital under the Director of Pharmacy with a listing of sites would enable the Board to know where all drugs were being distributed within a hospital. Mr. Karl Hohengarten RPh, Director of Pharmacy Services Swedish Hospital Medical Center, Seattle WA, discussed his satellite pharmacies and pharmacist operations at his hospital. Dr. Zoloth suggested that the Board request hospital pharmacists of the state to draft language for Board review and a formal regulation hearing to clarify and define hospital pharmacy licenses. It was suggested that Board Inspectors be trained in inspecting hospital pharmacy sites.

The Board reviewed newly published information on Phenylpropanolamine and related products that questions the efficacy and safety of diet aids. Mr. Osborne moved that the Board proceed with a regulation hearing to place diet aids in prescription only status. Motion passed. Dr. Raymond Ragland, Menley-James Laboratories, Philadelphia PA, was present for this discussion. Members asked for summary of testimony - written and oral - regarding PPA. It was requested that a draft regulation be prepared for informal hearing in October. Input is requusted from the Medical Association. The Senate Social and Health Services Committee has contacted the Board for any information regarding PPA containing diet aids.

Dr. Zoloth suggested a meeting with the Medical Association to discuss mutual medical problems: Schedule I status for Quaalude, triplicate prescriptions, as well as PPA diet aids. Dr. Zoloth shared a letter from Dr. George Aagaard MD, Professor of Pharmacology, UW Medical School. Dr. Aagaard is very concerned that hypertensive patients may be adversely affected by taking PPA containing diet aids without physicians' supervision.

The Board approved a revised statement containing the new time frames for sale of Schedule V cough syrups as prepared by the Washington State Pharmaceutical Association. The statement will be sent out with all Schedule V register books until a new printing of the books is available. This is the statement which is to be read by all purchasers at the time of a Schedule V sale.

Mr. Wayne Peterson RPh, Crista Community Center, appeared before the Board to discuss stocking of legend drugs (i.e., irrigation solutions) as floor stock before receipt of a prescriber's order. Mr. Osborne moved to allow Mr. Peterson as pharmacist to stock these legend drugs, pending review of Department of Social and Health Services requirements. Motion passed

Ms. Shirley Keck RN, representing the Washington State Nurses Association, was present and shared her concerns regarding nurse dispensing.

The Board expressed interest in a joint health professional-multi discipline committee to explore and deal with alcohol and drug abuse in health professionals, during October and November. Ms. Keck stated that the RN Association has formed a committee to inform the Association members regarding addiction and the handling of personnel. Ms. Keck recommended an article in the April issue of the American Journal of Nursing regarding drug use and abuse among nurses.

Mr. Osborne and Mr. Williams reported on the budget hearing for the Board of Pharmacy that was held in the Office of Financial Management in Olympia the previous day.

It was suggested that the Investigators meeting in December be held in conjunction with the Board meeting scheduled for December 9-10 in Olympia. Investigators will be asked for input on inspections and the inspection process.

Board members reported on meetings they had attended:

- -- Kitsap County Pharmaceutical Association - Members Zoloth and Osborne attended and discussed RN dispensing, Schedule V cough syrups and Dr. Romano's report on pharmacist/patient communication.
- -- State Pharmacy Association Long Range Planning Committee - David Palmer
- -- Drug Abuse Conference, Ellensburg WA - Executive Secretary Williams participated, speaking on the Legend Drug Act and the Controlled Substances Act.

Mr. Thompson moved to approve the August Board minutes. Motion passed.

Mr. Palmer discussed the role of the Board member as convenor in Ad Hoc committees. A Chairperson and minute taker should be selected by committee members, and the timetable for first draft established. The Board member should assist in setting the objectives of the committee.

Chairman Hennum recessed the Board meeting at 3:30 p.m., until the following day at 9:00 a.m.

Friday September 17, 1982 9:10 a.m.

Chairman Hennum reconvened the September Board meeting in the Burien Police Department conference room. All Board members and staff were present from the previous day.

The Board determined that it would place the triple combination drug - Ephedrine, Phenylpropanolamine, Caffeine in legend drug status, since the FDA has declared this combination to be a new drug. In addition to the "look alikes" containing this combination being manufactured and distributed to resemble legal controlled substance products, some companies are attempting to avoid state laws by placing this combination in a form which does not look like a controlled substance. Chairman Hennum asked that an emergency regulation be prepared by staff for the October Board meeting.

The Board met in Closed Session from 9:10 a.m. to 9:20 a.m. to review and sign disciplinary orders.

THE FOUR HUNDRED AND FORTY-SIXTH
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

October 14 and 15, 1982

Burien Police Department
(King County Precinct 4)
14905 6th Avenue SW
Burien, Washington 98166

Present:	Board Members
Lars Hennum	Chairman
Harold F. Osborne	Vice Chairman
Joseph J. Thompson	
David H. Palmer	
Dr. Arthur Zoloth	
Donald H. Williams	Executive Secretary
Barbara Phillips	Assistant Attorney General (Thursday)
Susan Jensen	Assistant Attorney General (Friday)
Mary-Helen Hansen	Clerk

The Board considered a request from Mr. Chia-Yao Hung, Oklahoma City OK, for approval of his clinical experience as internship credit. Mr. Hung is a graduate of the School of Pharmacy at Taipei Medical College, Taiwan. He will receive an M.S. degree in Nuclear Pharmacy from the University of Oklahoma in October and will be permitted to take the NABPLEX examinations in Washington in 1983. Mr. Osborne moved to allow 712 hours credit for Mr. Hung's clinical experience. Motion passed.

Dr. Dale Christensen joined Board members in a discussion of proposed new section Monitoring of Drug Therapy (definitions). The Board was concerned that the board scope of laboratory tests include but not be limited to analysis of body fluids, antibiotic sensitivities, drug levels, etc. Further discussion of this proposed section will be held at the November meeting.

The Board reviewed the Schedule V purchases and letter from Mr. Don Fadden regarding his medical condition, and letter from pharmacist Vicky McFarlane, Holiday Pharmacy, Seattle WA. It was felt that Mr. Fadden's condition should be reviewed by a physician and his medication be by prescription only.

Dr. Zoloth moved to grant the request of Ken Robbins RPh, Pendleton OR, that his practice of pharmacy as a pharmacist licensed in Idaho be accepted as Internship. Motion passed. Mr. Robbins passed the NABPLEX examinations in Washington in January 1982.

Mr. Osborne moved to accept the petition of William Mark Norris RPh, Tacoma WA, that his work in pharmaceutical sales be considered active practice of pharmacy. Motion passed. Mr. Norris has applied for reciprocity of his pharmacist license to Washington State.

Mr. Osborne moved to approve the request of Mrs. Billie A Kutzera RPh(inactive) that she be certified as a Level A Pharmacy Assistant. No further training will be required. Motion passed.

Dr. Zoloth moved to approve the Continuing Education credits of Roderick L. Newland RPh, Orofino ID, who has applied for reinstatement of his Washington State pharmacist license. Motion passed.

The Board welcomed Robert Coe MD, Washington State Medical Disciplinary Board, who is liaison member for the Board of Pharmacy. Dr. Coe was briefed on the proposed new section Monitoring of Drug Therapy.

The Board agreed to continue the reinstatement inquiry of Dale M. Robinson, pharmacist, Indianapolis IN, regarding his Continuing Education requirements, and ask for a record of CE hours completed.

The Board discussed the following proposals prepared by Mrs. Phillips at Board request:

-- Quaalude as Schedule I drug - Mr. Osborne moved to accept advice of counsel and ask the legislature to accept the proposed amendment to the Controlled Substances Act placing Quaalude in Schedule I. Motion passed. Dr. Zoloth asked that Parke-Davis drug manufacturing company be asked to comment and that the State Medical Association be notified.

-- Triple Combination as Legend Drug (Ephedrine/Phenylpropanolamine/Caffeine) AAG Phillips recommended no action as Ephedrine was now a Legend Drug (WAC 360-32-050 and -055). The Board agreed.

-- Phenylpropanolamine (PPA) as Legend Drug - The Board summarized information and hearings to date for Dr. Coe. Attorney Becky Bogard, Seattle WA, representing The Proprietary Association of Washington, D.C., and Dr. Raymond Ragland, Menley-James Laboratories, Philadelphia PA, reaffirmed safety and efficacy of the diet aid products when taken as directed as shown in tests and studies. Dr. Zoloth requested that a Task Force be convened to review all accumulated material and make recommendations to the Board. The Board is concerned with toxicity and the potential for harmful effect. Mr. Osborne moved to proceed with the Task Force and asked for Board members and staff to provide names of persons that would give a fair and equal representation of interested parties. Motion passed. The Task Force should include medical practitioners, The Proprietary Association, an independent pharmacist, a Board member, and representatives of consumer groups. The Board asked that the report be ready for the January Board meeting, with possible formal regulation hearing at the February Board meeting.

-- WAC 360-18-010 Licensing - Mr. Osborne moved to take the proposed amended rule to a regulation hearing. Motion passed. The amendment would clarify that licenses expire on the date given, and the grace period applies only to the penalty fee. This will be scheduled for a formal hearing at the December Board meeting and placed on the November Board meeting agenda for discussion.

-- WAC 360-16-260 Patient Medication Record System - Mr. Osborne moved for a December regulation hearing. Motion passed. This proposal would amend during a four year period beginning from the latter end of the one year suspension served pursuant to this Order, or the completion of any sentence of confinement arising out of the violations set forth above.

It is further ordered that prior to the return of his license to practice pharmacy, James Lee Clancy RPh, shall take and pass the jurisprudence examination given by the Board; and that he shall complete a drug abuse program approved by the Board; and that he shall provide to the Board a closing report from the drug abuse program and a report from another clinical psychologist or psychiatrist trained in substance abuse, each of which shall indicate that in his or her opinion the return of James Lee Clancy to the practice of pharmacy would neither endanger the public nor lead to a recurrence of the events which brought this matter before the Board.

The Board requested that the Assistant Attorney General presenting these disciplinary cases, schedule them closer together: for example, 9:00 a.m. and 10:00 a.m., or as soon thereafter as possible.

Dr. Zoloth shared a letter from an attorney, whose client is scheduled for a disciplinary hearing at the November Board meeting, asking that the Board not publicize the disciplinary decision, that such publication might jeopardize his client's current employment. The pharmacist in question has voluntarily surrendered his license to practice. The Board determined that they would publish all and any actions or punishments for the good of the profession.

Chief Inspector Charles James will attend the Computer Ad Hoc Committee meeting so that Board inspectors will be aware of the committee's actions.

The board discussed possible members for the PPA Task Force. Names suggested were John Chase MD, retired Dean of the UW Medical School, Alan E Nourse MD, George Aagaard MD, a representative of The Proprietary Association, John Bigelow, an endocrinologist, a psychologist, a toxicologist, Bennett Anderson RPh, an educator, and a representative consumer with a weight problem.

The Board commended two publications as useful resources for pharmacists: the two volume edition of the USPDI and the patient information booklet published by PHARMEX. It was suggested that these be mentioned in a future Newsletter.

Mr. Williams and the Board reviewed the Executive Secretary Policies and made the following determinations:

1. Policy Statements - retain
2. Administrative Responsibility - repeal
3. Vehicle Usage - retain, include overall vehicle policy
4. Continuing Education for Investigators - repeal
5. Conflict of Interest - revise. Dr. Zoloth expressed concerns about updating skills.
6. Witness Must be Present - retain
7. Narrative Report Required - place on agenda for Board meeting with Investigators, possible use of pass/fail rating system.
8. Per Diem for Drug Investigators - check with OFM
9. License Checks - combine with inspection process.
10. Compensatory Time - retain

THE FOUR HUNDRED AND FORTY-SEVENTH
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

November 18 and 19, 1982

Ridpath Hotel Arcade Room
W 515 Sprague Avenue
Spokane WA

1:05 p.m. OPEN MEETING

Present:	Board Members
Lars Hennum	Chairman
Harold F. Osborne	Vice-Chairman
David H. Palmer	
Joseph J. Thompson	
Dr. Arthur Zoloth	
Donald H. Williams	Executive Secretary
Barbara Phillips	Assistant Attorney General
Mary-Helen Hansen	Clerk
Willard Scott	Investigator

The Board discussed the status of the Phenylpropanolamine Task Force. Dr. John Chase has agreed to serve, but not to chair; Dr. Aagaard will review the information and then make a decision. Additional names were suggested. Attorney Rebecca Bogard, representing the OTC manufacturers of diet aids, and Dr. Raymond Ragland, Menley-James Labs, who were present for the discussion, suggested that Albert C. Eckian, M.D., Florida, be contacted to represent their clients on the Task Force. Dr. Zoloth will represent the Board. Task Force members will hold an organizational meeting after reviewing the material with regard to RCW 69.41.075 toxicity and safety. Dick Sherwood, Director of Pharmacy for Sacred Heart Medical Center, Spokane WA, reported on recent PPA related emergencies in his hospital. The Board requested that the following agencies or groups be contacted: sheriff's offices, school districts, associations of school counselors, and county health districts around the state for information concerning abuse of PPA diet aids in schools or with teenagers.

The Board reviewed correspondence from drug manufacturer Merck Sharp & Dohme advising that Redisol^{R} Tablets would no longer be sold in Washington State. The tablets were too soft for imprinting.

Information from Bob Rogers of Upjohn indicates that Upjohn's temporary exemption imprinting dates are being met.

The following licensee requests were considered and accepted or denied by motion:

- Depinder Grewel, Auburn WA, internship waiver request. 600 hours Internship credit granted provided he document his pharmacy experience in England.

Mr. Williams reported on the meeting with the RN Dispensing Committee on 11-12-82. WSPA and a committee from the Nurses' Association are gathering data concerning public need and availability of pharmacy services in the state. Data should be ready for a January 10, 1983, meeting in the Board of Nursing offices.

New CRN regulations may allow CRN's with prescriptive authority who are registered with the Drug Enforcement Administration and the Board of Pharmacy to prescribe Schedule V Controlled Substances. The RN Board did not make "indicated use" a requirement for the prescription document. The Board of Pharmacy testified against the deleting of this requirement. RN's felt it was a standard of good practice, but since other prescribers did not need to put the indicated use on the prescription, they should not be required to. Board members suggested that the Board of Nursing circulate the new C-V regulations to offset abuser activity.

AAG Phillips suggested adoption of a proposed amendment to WAC 360-36-010 on an emergency basis with regulations adopted on a permanent basis later to establish fees for licensing CRN's to prescribe Controlled Substances.

Dr. Zoloth moved to adopt WAC 360-36-010 sub (2) adding new sections (k) and (l) as drafted by Mrs. Phillips, to allow for Board registration and licensing of CRN's with prescriptive authority to prescribe Schedule V Controlled Substances. Motion passed.

WAC 360-36-010, sub (2)

(k) $15.00 for application for Certified Registered Nurse with prescriptive authorization;

(l) $10.00 for the annual renewal for Certified Registered Nurse with prescriptive authorization.

The Board meeting recessed at 4:15 p.m. until 7:00 p.m. for a night meeting with the Spokane Pharmaceutical Association.

Chairman Hennum reconvened the evening meeting at 7:20 p.m. All Board members and staff were present. Chairman Hennum asked for a moment of silence for Pharmacist Don Katterman of Seattle WA, past president of WSPA, who died that morning.

Mr. Osborne reported on the new drug approval process of the FDA, due to take effect next spring. The new process should speed up processing of applications, provide better survellience, and permit approval and review of foreign drugs originally introduced in a foreign country.

Dr. Zoloth summarized previous Board discussion concerning PPA containing diet aids and look alikes and the formation of the PPA Task Force and a second area of concern, hospital pharmacy licensing problems and possible resolution - for the benefit of the Spokane pharmacists.

Mr. Williams and Chairman Hennum gave an overview of the Sunset review and ramifications for the Board and the practice of pharmacy.

CRN prescribing, C-V sales, and pharmacist prescriptive authority were subjects reviewed for the audience.

THE FOUR HUNDRED AND FORTY-EIGHTH
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

WEA Building - 319 E. 7th Avenue
Olympia, Washington 98504

December 9 -10, 1982

Board Members:

Lars Hennum	Chairman
Harold F. Osborne	Vice-Chairman
David H. Palmer	
Joseph J. Thompson	
Dr. Arthur Zoloth	

Staff:

Donald H. Williams	Executive Secretary
Barbara Phillips	AAG, Counsel to the Board
Mary-Helen Hansen	Clerk
Board Investigators	David Campbell, Charles James, Frank Bracelin, Willard Scott, Robert Miller, Richard Morrison, Hobart Ashmore
Susan Masters	Intern Desk
Ray Olson	Executive Director, Washington State Pharmaceutical Assn.

9:30 a.m. CLOSED SESSION Meeting with Board Investigators

11:00 a.m. OPEN MEETING

The Board denied a request by Ms. Sean Kelleher RPh (Wisconsin), Yakima WA, for transfer of NABPLEX scores. Wisconsin did not forward her scores in response to a request by the Washington Board. Ms. Kelleher is prepared to take the Full Boards in January 1983.

Greg Hovander RPh, Valley View Clinical Pharmacists, Monroe WA, presented a proposed protocol for the distribution of drugs by nurses. Mr. Hovander discussed possible licensing and approval for pharmacists to enter into a contractual agreement and run as a satellite pharmacy any kind of formal setting where a Registered Nurse is distributing drugs. No Controlled Substances would be prepackaged and stocked. The RN would be serving as the pharmacist's agent. Places of distribution would exist only where no other pharmacy services were located within ten miles of that site. The Board will review Mr. Hovander's protocol for procedures applicable to resolution of the RN dispensing issue now under discussion with the RN Board.

Chairman Hennum opened the Formal Regulation Hearing at 1:00 p.m.

WAC 360-40-060 Submission of Condoms for Testing. New Section

Mr. Palmer moved to adopt. Motion passed.

WAC 360-40-070 Condom Testing. New Section

Mr. Osborne moved to adopt. Motion passed.

WAC 360-40-080 Suspension or Revocation of Prophylactic Licenses. New Section

Mr. Osborne moved to adopt. Motion passed.

WAC 360-44-020 Definitions (Public Records Disclosure)

Mr. Osborne moved to adopt as amended. Motion passed.

WAC 360-44-040 Operations and Procedures.

Mr. Osborne moved to adopt as amended. Motion passed.

WAC 360-44-090 Copying.

Mr. Osborne moved not to adopt the proposed amendment. Motion passed.

Attachment 1. WSR 82-22-087 Notice of Intent to Adopt, filed 11/3/82

Attachment 2. WSR 83-01-083 Rules Adopted, filed 12/17/82

End of Regulation Hearing

Mr. Williams reviewed the status of Schedule V cough syrup sales since the new regulations were adopted: Pharmacies are sending in the single register sheets as required; there does seem to be a reduction in sales by many pharmacies. Mr. Ray Olson, WSPA, offered to supply monthly statistics from the sales of books by his office. It was also suggested that new books might have 10 lines to a page instead of the present 20. The Board requested statistics on the C-V sales by high volume pharmacies.

PPA Task Force - Mr. Williams reported that a packet of information has been prepared for all members. All information is to be channeled through the Board office. John Bigelow, Wayne Kradjan RPh, and Bennett Anderson RPh have accepted appointments to the Task Force. "Look alike" advertising received in the Board office no longer lists PPA as an ingredient, just ephedrine and caffeine since the FDA has outlawed the triple combination.

Computer Regulations Task Force - Mr. Palmer reported that he was pleased with the progress of the committee, and that they were probably two to three months away

THE FOUR HUNDRED AND FIFTY-FIRST
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

March 16 and 17, 1983

King County Precinct 4
14905 6th Avenue SW
Burien, Washington

Board Members Present:

Lars Hennum, Chairman
Harold F. Osborne, Vice-Chairman
David H. Palmer
Joseph J. Thompson
Dr. Arthur Zoloth

Staff:

Donald H. Williams, Executive Secretary
Jeffrey O. C. Lane, Assistant Attorney General
Mary-Helen Hansen, Clerk

Others:

Mel Gaumer, Menley and James Laboratories
Jeff Smith, Washington State Medical Association
Becky Bogard, Thompson Medical Company
Joan Cohee
Herk DesForges, Payless NW
Karl Hohengarten, Swedish Hospital
Doug Meeman, Group Health
Holly Streeter, Washington State Pharmaceutical Association
Kathy Moritis, RN, Washington State Nurses Association

The meeting was opened at 9:20 a.m. by Acting Chairman Harold Osborne.

I. Board Member Reports

1. PPA Task Force - Dr. Zoloth

More testimony is needed, public hearings should be held, and a procedure for reviewing the volume of data developed. A chairman should be selected before the first meeting to enable Task Force members to begin deliberations at once. A representative of the high school counselors group is needed. Lobbyist Becky Bogard will represent Thompson Medical. Menley and James Laboratories will be represented by Mel Gaumer. Other members include: Drs. Chase, Aagaard, Eckian, and Robertson; Pharmacists Evelyn Benson or Bennett Anderson and Wayne Kradjan; and John Bigelow, retired Executive Director of the State Hospital Association.

Copies of a new report regarding toxicity were requested. Staff was directed to formalize the Task Force and set the first meeting. Dr. Zoloth agreed to act as convenor and represent the Board.

The Board reviewed a letter from John Morgan, MD., Medical Professor and Director at the Pharmacology Program, Sophie Davis School of Biomedical Education, City College of New York. Dr. Morgan objected to the Board minutes of June 24, 1982, reporting his presentation on "look-alikes" before the Board. Dr. Morgan's letter will be made available to the Task Force. Dr. Zoloth moved to move on to another topic. Motion passed. The Task Force will be made aware of the Board's actions and that the letter was given full consideration.

2. Continuing Education Committee - Joe Thompson submitted a report of the November 9, 1982, meeting of the CE Committee prepared by Sharon Sullivan RPh. Chairman. The Committee recommended changes to the present system of approving CE programs, asked for more participation by Board members, and the appointment of new hospital pharmacy representatives.

   The Board will provide guidelines to the Committee and review the membership, appointing new members as needed. Joe Thompson and Don Williams will review the report and the membership. The procedures for 30 day prior approval of CE programs was suggested as a NEWSLETTER item.

3. Board Regulations and Drug Recall - Art Zoloth

   Changes should be made in WAC 360-16-150 to allow pharmacists to accept drugs for return to manufacturers during a national recall, and to permit unused medications in unit dose pachages to be returned to pharmacies for credit where the unit of use has not gone out of the control of individuals either dispensing or administering.

   Dr. Zoloth moved that AAG Lane prepare an emergency regulation amendment to WAC 360-16-150 for the April Board meeting with permanent adoption to be filed for early hearing. Motion passed.

Lars Hennum arrived at 9:55 a.m. and assumed the Chair.

4. Ad Hoc Group, Drug Diversion and Substance Abuse in Institutions

   Dr. Zoloth is convening a meeting of representatives from the medical and RN disciplinary boards, DEA, hospital administration, and the State Hospital Association, employee assistance programs, and the legal department of the State Medical Association to discuss the problem and to form a committee for study and education that would prepare a formal set of guidelines for reporting and referral. It was suggested that the Washington State Pharmaceutical Association be contacted to send a representative as they have begun an impaired pharmacist program. Rob Menaul, State Hospital Association, will coordinate the program. Don Williams will attend the March 24, 1983, meeting.

   The Board requested an update on substance abuse for a future meeting.

THE FOUR HUNDRED AND FIFTY-SECOND
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

April 20 and 21, 1983

King County Precinct 4
14905 6th Avenue SW
Burien, Washington 98168

Board Members Present:

Harold F. Osborne, Chairman
David H. Palmer, Vice-Chairman
Joseph J. Thompson
Dr. Arthur Zoloth
Lars Hennum

Staff:

Donald H. Williams, Executive Secretary
Barbara Phillips, Assistant Attorney General
Mary-Helen Hansen, Clerk

Others: See attached list

The four hundred and fifty-second meeting of the Washington State Board of Pharmacy was called to order at 9:05 a.m. by Chairman Harold F. Osborne. In opening remarks as newly elected Chairman, Mr. Osborne reviewed the recent accomplishments of the Board and the goals and challenges it faces today, including the Sunset review by the Legislative Budget Committee.

9:15 a.m. Chairman Osborne opened the Formal Regulatory Hearing:

> Notice is hereby given in accordance with the provisions of RCW 34.04.025 that the Washington State Board of Pharmacy intends to adopt, amend, or repeal rules concerning:
>
> Adding New Sections WAC 360-12-150, 360-13-100, 360-16-300; adding New Chapter 360-33 WAC, 360-33-050; and repealing 360-23-040.
>
> Notice No. WSR 83-06-074 was filed with the code reviser March 2, 1983.

WAC 360-13-100 Provisions for Continuity of Drug Therapy for Residents was considered by the Board.

The following persons testified byfore the Board:

- -- Fran Moellman, Manager, Operations Program, Bureau of Nursing Home Affairs/DSHS, Olympia CON
- -- Sandie Beeman RPh, Washington State Pharmaceutical Assiotion PRO

WAC 360-23-040 is hereby repealed. Attachment #6

End of Regulatory Hearing

II. Phenylpropanolamine

Leonard Albert, MD,Ph:D.(Pharmacology), MPH, related his experience and knowledge of adverse reactions to Phenylpropanolamine, and his concern with the OTC status of PPA. Dr. Albert felt that PPA should be a scheduled drug with controlled prescribing such as the laws enacted for amphetamines. Dr. Albert has agreed to serve on the PPA Task Force.

III. PPA Task Force

Task Force nominees are to be contacted and a meeting date set. The Board requested that the Task Force report by the July Board meeting. The Chairman should be selected before the first meeting. The Task Force is to be given copies of the statute. Terms used in the statute are mandatory on what the Board shall consider and what the determination shall be based on. Efficacy may be considered but would not be enough under the statute for the Board to place PPA in prescription only status, according to Barbara Phillips, AAG. Consumer representation is still needed, and a physician who has actually treated patients for weight control would be a wise addition to the Task Force.

IV. Pharmacy Assistants in a Hospital Pharmacy While the Pharmacist is Not Present - Valley General Hospital, Monoe WA.

Steve Erickson RPh, Director of Pharmacy, Carol Johnson RPh, Alvina Hereth RN/Director of Nursing Services, and Lane Savitch, Hospital Administrator, explained hospital procedures and pharmacist availability to the pharmacy site.

The Board determined that the present supervision procedure with regard to Pharmacy Assistants at Valley General Hospital pharmacy is not in violation of WAC 360-52-010.

Dr. Zoloth moved that the "C" Grade be removed and the inspection continue under JCH rules. Motion passed.

If a similar situation occurs during a hospital pharmacy inspection, Board Inspectors are to be asked to bring the matter to the Board and provide a copy of the most recent JCH report on the hospital.

V. Substance Abuse Meeting - Don Williams

Representatives of the health professions and hospital administration were made aware of the extent of the problem and discussed ways to

THE FOUR HUNDRED AND FIFTY-THIRD
MEETING OF THE WASHINGTON STATE
BOARD OF PHARMACY

May 11-12, 1983

Conference Room
Mason Clinic East
13014 - 120th NE
Kirkland WA

Board Members Present:

David H. Palmer, Acting Chairman
Joseph J. Thompson
Dr. Arthur Zoloth
Lars Hennum

Donald H. Williams, Executive Secretary
Barbara Phillips, Assistant Attorney General, Counsel
Mary-Helen Hansen, Clerk

Others: See attached list

The four hundred and fifty-third meeting of the Washington State Board of Pharmacy was called to order at 9:08 a.m. by Acting Chairman David H. Palmer.

I. Curriculum Changes - School of Pharmacy, University of Washington - Lynn Brady, Ph.D., Director, Academic and Student Programs

The new curriculum allows for flexible choices of externships. Didactic, required courses are scheduled for the first two years and electives are scheduled for the third year. The basic philosophy has not changed. Board members stressed the need for the following:

1) A required law class in the spring term at the end of the pharmacy studies program to present the new laws and regulations enacted and to prepare students for the Jurisprudence Examination.

2) More involvement by Board members and staff with students and curriculum, seminars, lectures, etc.

3) Importance of the behavioral science course to prepare students for contact with the public. Student development is weak in this area, particularly with regard to community pharmacy. A possible change in the time this class was offered in the curriculum was suggested.

4) Better communications and contact with curriculum and internship programs at the College of Pharmacy, Washington State University.

Washington State University College of Pharmacy will be asked to make a presentation on their pharmacy program at a future Board meeting.

II. Emergency Outpatient Medication/Proposed Regulation - William Baluch, Chief Pharmacist, Harborview Medical Center, and spokesman for the Professional Affairs Council, The Washington State Society of Hospital Pharmacists.

The proposed regulation would be placed in chapter WAC 360-17 Hospital Pharmacy Standards, and would allow the pharmacy to maintain control of modest amounts of prepackaged medication for dispensing after hours. It is modeled after the State of Oregon regulations on this topic. The proposed regulation would allow RN dispensing in emergency rooms after hours and provide a controlled system of medicine distribution.

Dr. Zoloth moved that the draft regulation be prepared for regulatory hearing before the Board at the July meeting. Motion passed.

The committee was complimented on its work. It was suggested that the committee contact the Emergency Room Nurses group for an expression of their needs, before final draft was submitted.

Sandie Beeman, RPh, reported that the Interprofessional Affairs Committee, Washington State Pharmaceutical Association, had not addressed the problem of Controlled Substances and suggested that the Board look at that area at the regulation hearing, because of the state and federal regulations regarding Controlled Substances.

III. PPA Task Force - Initial Meeting - Art Zoloth

Dr. Zoloth reported on the preliminary meeting at Virginia Mason Hospital. Mr. John Bigelow, retired Executive Director of the State Hospital Association, who will Chair the Task Force, Len Albert, MD, and Don Williams met with him to work out the organization of the Task Force and informational data they would be asked to review. The focus of the review will be safety. Don Williams will read the laws and rules giving authority to the Board to act in this matter. It was the consensus of the Task Force members present that there may be a conflict of interest for Dr. Eckian, whose expenses were being paid by the OTC manufacturers of diet aids, to remain as a member of the Task Force. He should appear as an expert witness instead. Mr. Gaumer objected to this suggestion on behalf of Menley and James Laboratories.

After discussion, Mr. Hennum moved that the Board reinforce its previous statement that Dr. Eckian be a part of the Task Force. Motion passed.

The first full meeting will be held on May 26, 1983, at Virginia Mason Hospital, Seattle, beginning at 7:00 p.m.

Don Williams reported that a study on diet aids conducted by Pharmacy Times seems to be the basis for the current TV advertisement by Thompson Medical that more pharmacists recommend Dexatrim^R than any other product. 3000 pharmacists were surveyed, 807 responded, 20.8% recommended Dexatrim^R, 9.2% recommended Diatac^R. 10.4% recommended nothing. 24% did not answer. ~~Thus 8 out of 10 Pharmacists did not recommend Dexatrim^R.~~

The Board Office has received a number of adverse comments to this T.V. advertisement.

PPA is also showing up on the [redacted] report according to Dr. Zoloth.

APPENDIX 3

SUBMITTED FOR THE RECORD

BY

THE FOOD AND DRUG ADMINISTRATION
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR THE HEARING BEFORE THE

SUBCOMMITTEE ON HEATH AND LONG-TERM CARE
SELECT COMMITTEE ON AGING
HOUSE OF REPRESENTATIVES

JULY 21, 1983

The following statement is provided for the record of the hearing of the Subcommittee on Health and Long-Term Care, Select Committee on Aging, U.S. House of Representatives, July 21, 1983. We also presented testimony at a joint hearing before the House and Senate Aging Committees on June 28, 1983 on the more general subject of the safe use of drugs in older Americans.

OTC Drug Review

We were requested by the Subcommittee staff to discuss our over-the-counter (OTC) drug review process, the drug ingredient phenylpropanalomine (PPA) and our adverse drug reaction (ADR) reporting system. OTC drugs are an important part of health care in the United States affecting the elderly as well as the general population. These drugs provide consumers with products for the treatment of minor conditions without the need for costly medical services. Because they may be used without medical supervision, it is essential that OTC drugs not only be generally recognized as safe and effective, but also that they provide adequate directions for use to permit consumers to realize their benefits without significant risk of adverse side effects. In 1972, Food and Drug Administration (FDA) established the over-the-counter drug review to assure that OTC products, then on the market, or introduced in the future, meet these standards of safety and effectiveness.

Before the establishment of the OTC drug review, there had never been an evaluation of the available scientific evidence to demonstrate safety and effectiveness for most OTC drugs. Prior to passage of the 1962 amendments to the Federal Food, Drug, and Cosmetic Act which established the legal obligation to demonstrate effectiveness, drugs entering the marketplace needed only to be shown to be safe. Before 1962, most OTC products were marketed without prior Agency clearance because it was assumed that OTC drugs did not pose significant safety problems and were, therefore, generally recognized as safe. FDA regulated OTC drugs mainly through court actions against specific products using the statutory prohibitions against misbranding and adulteration. However, this approach was found inadequate to bring about systematic application of the effectiveness provisions of the 1962 amendments to the estimated 300,000 marketed OTC products with annual sales of nearly four billion dollars. In its application of the 1962 effectiveness amendments, FDA was assisted by the National Research Council of the National Academy of Sciences. Beginning in 1966, the Council evaluated about 4,000 products, including 512 OTC drug products that FDA had approved for marketing on the basis of safety only. About 300 of these OTC products were found to be ineffective for one or more of their labeled uses. FDA decided it was time to take a further look at the OTC marketplace.

In deciding how to conduct the OTC drug review, the Agency had two choices: It could review each of the OTC products individually and, by separate court actions, move against each violative product, a process that would take at least several decades to complete, even if the market remained static and new products did not enter the market. Or it could establish rulemaking procedures to write monographs for each therapeutic class of OTC drugs. Because it was estimated that there were only about 500 active drug ingredients contained in OTC drug products, the Agency decided that rulemaking by active drug ingredients within therapeutic classes would be the most cost effective, efficient, and equitable procedure.

The review began in 1972 with all OTC drugs being classified into 25 therapeutic categories (e.g., antacids, laxatives), and two miscellaneous categories. The OTC drug review program is a three-phase rulemaking process culminating in the establishment of standards for the different nonprescription therapeutic drug categories. The first phase was accomplished by advisory review panels, each of which included as voting members a pharmacist, a pharmacologist or toxicologist, physicians, and other scientifically qualified individuals, as well as nonvoting technical liaison members representing consumer and drug industry interests. The panels were charged with reviewing the ingredients in nonprescription drug products to determine whether these ingredients could be generally recognized as safe and effective for use in self-treatment. They were also charged with reviewing claims and recommending aporopriate labeling, including therapeutic indications, dosage instructions, and warnings about side effects and preventing misuse.

According to the terms of the review, the panels classified ingredients in three categories as follows:

Category I - Generally recognized as safe and effective for the claimed therapeutic indications;

Category II - Not generally recognized as safe and effective or unacceptable indications;

Category III - Insufficient data available to permit final classifications.

Based on the information received, and on the expertise of the panelists and on their deliberations, each panel prepared one or more reports to the Commissioner containing its conclusions and recommendations, including a proposed monograph which describes the conditions under which a drug is considered safe and effective and properly labeled for OTC use. Thereafter, the Commissioner then publishes each report and recommended monograph in the Federal Register as an Advance Notice of Proposed Rulemaking, and invites public comment. Under FDA's OTC procedures, panel reports are published exactly as received. If a report involves an issue of special significance, FDA's views are expressed in the preamble to the report. After review of the public comments, a tentative final monograph--the second phase--(proposed rule) is published with opportunity for further public comment and oral argument before the Commissioner. The publication of final regulations in the form of drug monographs is the third and last phase of the review process.

The panel phase of the OTC drug review extended over a period of almost 10 years, with over 300 individuals participating in this unprecedented project. The first panel meeting was held in February 1972, by the panel convened to review nonprescription antacid ingredients. The last meeting convened in October 1981, at which time the panel charged with reviewing ingredients for miscellaneous internal use finished its review of menstrual products. Between 1972 and 1981, an initial determination was made of the safety and effectiveness of ingredients for therapeutic claims ranging from antiflatulents to antimicrobials, and from hair restorers to pinworm remedies. These findings were based on a review of 14,000 volumes of data submitted largely by manufacturers, but also by concerned consumers, pharmacists, and other interested parties. The panel's judgments were also based on their own clinical experience and expertise, on marketing experience of ingredients, and on both controlled and uncontrolled clinical trials. The panels also relied on the published literature, but isolated case reports, random experience, testimonials, and reports lacking sufficient details to permit scientific evaluation were not considered.

Overall, FDA received nearly 60 reports from the panels. These reports and monographs summarizing the panels' recommendations to the Commissioner of Food and Drugs were published in the Federal Register.

Although the OTC review is still several years away from completion in terms of final regulations, it has already had an impact on the public's attitude toward self-medication and on the marketplace. Publicity given the review by the news media has resulted in a heightened public awareness of nonprescription drugs and their usefulness in health care.

The review has also generated substantial scientific research that has produced impressive amounts of new data on nonprescription drugs. Approximately one third of the ingredients reviewed by the panels were shown to be safe and effective for their intended uses. Additional data are being developed on many of the remaining ingredients in an effort to demonstrate their safety or effectiveness. However, ingredients that cannot be shown to be both safe and effective for their intended uses have been, and are continuing to be, dropped from formulations and will eventually disappear from the marketplace.

A few ingredients were found to be so unsafe by the panels that they were removed from the market before completion of the full rulemaking process. In these special cases, the panels' recommendations were published as the Agency's proposals to expedite market removal. For example, the antimicrobial ingredient hexachlorophene was removed from the nonprescription drug market in 1972 because of potential neurologic toxicity. In 1975, other antimicrobials, including tribromsalan and similar halogenated salicylanilides that were found to be photosensitizing ingredients, were removed from the market; and, in 1977, zirconium, widely used in antiperspirants, was removed from "aerosolized" drug and cosmetic products because of the potential for particulate zirconium to cause granuloma formation in the lungs.

In June 1979, the Agency initiated a recall of all oral and topical products containing methapyrilene from the OTC market because a National Cancer Institute study provided data implicating this ingredient as a potential human carcinogen.

PPA (Phenylpropanolamine)

We are aware that the Subcommittee is especially interested in OTC preparations containing PPA. We would, therefore, like to provide you with background information on this drug.

Phenylpropanolamine is available to the public in a number of products. It is available as a prescription drug, and as OTC medication, in the form of potent stimulants, in the form of cough-cold-allergy preparations and appetite suppressants.

Two different advisory review panels have made recommendations to the Agency with respect to PPA. The advisory review panel report on OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products was published in the Federal Register of September 9, 1976 (41 FR 38312). That Panel concluded that PPA and its various salts were generally recognized as safe and effective (Category I) for oral use as a nasal decongestant. The panel recommended that the adult dose for immediate-release dosage forms be 25 mg every 4 hours and for sustained-release dosage forms was 50 mg every 8 hours, not to exceed

150 mg in 24 hours in either case. The Panel recommended that the drug be administered for no longer than 7 days.

In the Federal Register of October 28, 1977 (42 FR 56756) the Agency subsequently deleted from the OTC drug review the provision for a sustained-release preparation. Consistent with Agency policy (21 CFR 200.31) sustained-release dosage forms containing an amount of active ingredient in excess of what is considered to be generally recognized as safe in a single-immediate release dosage unit are regarded as new drugs and require the approval of a new drug application before marketing.

The tentative final monograph (proposed rulemaking) for nasal decongestants is currently being developed and is close to completion. The Agency's conclusions regarding the use of phenylpropanolamine in OTC cough/cold drug products will be initially presented in that document.

The OTC Advisory Review Panel on Miscellaneous Internal Drug Products also reviewed PPA for its use in OTC weight control drug products. Its conclusions were published in the Federal Register of February 26, 1982 (47 FR 8466). PPA hydrochloride was judged by the Panel to be generally recognized as safe and effective (Category I) as an appetite suppressant at a dose of 25 to 50 mg before meals 3 times daily with a maximum of 150 mg per day for either immediate-release or sustained-release dosage forms. The Panel also recommended that weight control preparations be used for no longer than 3 months. Prior to the Panel's report, PPA had been available in OTC weight control products in an immediate-release dose of up to 37.5 mg and a time-release dose of up to 75 mg, with the total daily dose not to exceed 75 mg in either case.

Between the time the panel's report was forwarded to the Agency (March 1979) and its publication in the Federal Register (February 1982), the Agency became aware of several reports indicating that PPA doses higher than those currently on the market (but within the higher range recommended by the panel) cause elevation of blood pressure. The preamble to the published report highlighted these data and also discussed other studies which showed that current marketed dosages produced no such effect. The preamble indicated that further studies were needed to establish a suitable safe dose level for PPA. The Agency concluded that further studies appeared necessary to determine the extent to which PPA induces hypertension in normotensive patients or aggravates pre-existing hypertension, and whether PPA interacts with aspirin or other similarly acting drugs at the dose levels recommended by the Panel. The Agency concluded that until the safety questions are resolved, PPA would not be permitted to enter the marketplace at dosage levels higher than those currently on the market. The Agency believes that this position was scientifically justified by the evidence available at that time.

In response to this controversial issue, the Agency has received numerous comments on the Advance Notice of Proposed Rulemaking and is in the process of evaluating them. In addition, the Agency is continuing to monitor any and all available data and information on PPA. Because of the complicated nature of this issue, the tentative final monograph for OTC weight control drug products is some time away from publication. Resolution of the PPA issue has also delayed final processing of the OTC nasal decongestant tentative final monograph. If any new information shows that any of the existing uses, dosage levels, or dosage forms of PPA pose safety risks, the Agency will take appropriate regulatory action.

Post-Marketing Surveillance/Adverse Drug Reactions

Reports of adverse drug experiences received by a drug manufacturer are required, by law and regulation, to be periodically submitted to the FDA. These requirements, however, only apply to drugs which are the subject of approved new drug applications (NDAs). For the most part, these are prescription drug products.

There is no such reporting requirement for OTC drugs since most OTC drugs have not been approved via the new drug approval process. As part of its ongoing program for monitoring the safety of drugs marketed in the United States, the FDA does, however, solicit reports of adverse drug experiences from consumers, physicians and other health professionals. These reports are voluntarily submitted to the FDA, or to a drug manufacturer who, if the drug has an NDA, must then submit them to the FDA where they are evaluated as a potentially emerging drug safety problem. Although underreporting is substantial with such voluntary reporting systems, the information available is probably a fairly accurate indication of trends of the incidence of adverse events with any given drug.

As stated above, the Agency is continuing to monitor all available data and information on phenylpropanolamine. This includes adverse drug reaction reports and other surveillance activities.

Before discussing these; however, we would like to comment beriefly on phenylpropanolamine drug use.

Although precise estimates of actual population exposure to PPA are unavailable because many of these products are purchased OTC and seldom prescribed, data from a variety of sources such as IMS America audits, Pharmaceutical Data Services and the Michigan/Minnesota Medicaid system suggest that the level of exposure is considerable.

The voluntary case reporting program continues to provide reason for concern regarding the safe use of PPA as an OTC drug. It remains difficult to define the extent and significance of the problem although there are ongoing efforts using FDA contract resources to address this area. The FDA is coordinating two studies which are looking at the risk of serious events such as intracranial bleeding, i.e. stroke, in persons exposed to PPA. One study is being carried out in the Michigan/Minnesota Medicaid system; the other in the Puget Sound HMO. Results from these studies should be available in late 1983.
The Agency is also in the process of funding a study of toxicity of PPA and other stimulants in animals, specifically a rat model. The administrative details have not yet been completed, but should be in the coming month, and the investigator should be able to provide data on the ability of these agents to contribute to subarachnoid hemorrhage, the major morbid effect of PPA.

Thus, we are carefully assessing, and will continue to assess, the complex issue of the safety of this drug. Also, because of the seriousness of the adverse reactions associated with the use of PPA products, all of the new data being generated are being reviewed by FDA's Division of Cardio-Renal Drug Products, whose staff includes specialists in the field of cardiovascular medicine. In addition, should the need arise, this issue could also be taken before that Division's standing advisory committee on Cardiovascular-Renal Drugs.

Conclusion

In conclusion, we remain committed to the concept of providing safe and effective medications OTC. It cannot be overemphasized that OTC drugs are vital to the health care system in this country, especially when one considers the rapidly accelerating costs of providing and obtaining adequate medical care.

MEDICAL SOCIETY OF THE STATE OF NEW YORK
420 LAKEVILLE ROAD, LAKE SUCCESS, N.Y. 11042 (516) 488-6100

EDWARD SIEGEL, M.D.
EXECUTIVE VICE-PRESIDENT

August 2, 1983

The Honorable George C. Wortley
House of Representatives
Washington, DC 20515

Dear Congressman Wortley:

At its most recent meeting on June 16, 1983, the Council of the Medical Society of the State of New York considered the dangers inherent in the unrestricted sale of phenylpropanolamine hydrochloride in diet pills or liquids. The Council, recognizing the great potential for the abuse of this substance, adopted a resolution which called for the making of phenylpropanolamine hydrochloride a prescription drug and directed that the New York Congressional Delegation be informed of this position.

Please be advised, therefore, that the Medical Society of the State of New York supports all appropriate Federal legislation which would make phenylpropanolamine hydrochloride a prescription drug.

We respectfully request, furthermore, on behalf of the more than 25,000 members of the Medical Society of the State of New York, that you lend your support to Federal legislation which would make phenylpropanolamine hydrochloride a prescription drug.

Thank you very much for your kind attention in this matter.

Sincerely,

Edward Siegel, M.D.
Executive Vice-President

S/H/

THE PROPRIETARY ASSOCIATION
1700 Pennsylvania Avenue N.W./Washington D.C. 20006/Phone (202) 393-1700

August 17, 1983

William Halamandaris
Majority Staff Director
Subcommittee on Health and Long-Term Care
House Select Committee and Aging
715 House Office Building, Annex 1
Washington, D.C. 20515

Dear Bill:

Pursuant to our telephone conversation, please find enclosed a copy of The Proprietary Association's Statement for inclusion in the official hearing record of the Subcommittee's July 21 hearing on "The Safety and Efficacy of OTC Drugs."

We certainly appreciate this opportunity to provide the Subcommittee with this Statement and hope that the information will be helpful in its deliberations.

Sincerely,

Allan R. Rexinger
Director of Legislative Relations

Enclosure: Statement of The Proprietary Association

ARR/bl

THE PROPRIETARY ASSOCIATION
1700 Pennsylvania Avenue N.W./Washington D.C. 20006/Phone (202) 393-1700

Statement of The Proprietary Association

Public Hearing on "The Safety and Efficacy of OTC Drugs"
Before the Subcommittee on Health and Long-Term Care
Select Committee on Aging
U.S. House of Representatives
July 21, 1983

Preface

The following statement is submitted for inclusion in the official hearing record on behalf of The Proprietary Association, a 102-year-old trade association, the active members of which are engaged in the manufacture and distribution of nonprescription or over-the-counter (OTC) medicines. OTC medicines are intended for use by the consumer for the treatment of minor, generally self-limiting ailments or disorders, such as headache, acid indigestion, colds symptoms, minor skin irritations, and so forth. They include such products as St. Joseph's Aspirin®, Vicks Cough Syrup®, Noxzema Skin Cream®, Tums®, and many others. The Association's members are subject to the Federal Food, Drug and Cosmetic Act [21 U.S.C. 301, et seq.], administered by the Secretary of Health and Human Services and the Food and Drug Administration.

I. Self-Medication is Vital to the Nation's Health Care System

Nonprescription medicines are the first line of defense in the nation's total health care system. These products are composed of ingredients whose pharmacological actions are generally well understood and there is a wide margin of safety in their use. They are used by consumers for the treatment of symptoms and illness and injury without the supervision of a health professional. The Food and Drug Administration's Commissioner, Arthur Hull Hayes, Jr., M.D., has spoken of the importance of nonprescription medicines:

> "Nonprescription drugs occupy an essential place in health care. The ability of Americans to select, buy and use over-the-counter products to treat conditions that do not require the attention of a doctor is, I believe, a cornerstone of our health care system and of our policy for consumer health protection.
>
> Our job, both industry's and FDA's, is to see that the cornerstone remains firmly in place, and that means that the proprietary drug industry needs to maintain its high standard in the quality, manufacture, and marketing of

REPRESENTING MANUFACTURERS OF NONPRESCRIPTION MEDICINES

> OTC drugs, and that FDA needs to be both vigilant and efficient in carrying out its responsibilities as the public agency charged with regulating OTC drugs."[1]

Responsible self-medication performs valuable and even crucial functions for individuals, the health care system, and the economy. For the individual, it is a familiar, inexpensive, and convenient method of treating common discomforts. For the health care system, it provides a shield against a deluge of visits to health professionals for minor disorders. For the national economy, it helps contain the demand for primary care and, in turn, the total cost of formal medical services.

The U.S. Department of Commerce publication entitled U.S. Industrial Outlook, for example, underscores the significance of OTC medicines in the nation's health care scheme. The statement, true in 1978, has even more validity today.

> Self-medication with proprietary drugs is a significant factor in the U.S. health care scheme. Escalating costs of health care create a greater need for low cost self-medication than ever before. Seventy-five percent of all illnesses and injuries are initially treated through self-care and OTC medication. If only a small percentage of self-treatment was shifted to medical practitioners, the patient load would disrupt the U.S. health care system.[2] (emphasis added).

Total retail sales of OTCs in 1982 were $6.2 billion. This amounts to about $26.43 per capita annually or $.07 per day. This compares to 1982 per capita annual expenditures of $32.78 for candy and gum, $44.49 for cosmetics and toiletries, $68.38 for prescription drugs, $94.69 for tobacco and $123.44 for alcohol.[3]

II. The OTC Review

The federal Food and Drug Administration currently is reviewing the safety, effectiveness, and labeling of virtually all OTC drugs in the OTC Review. That Review represents the most thorough, extensive, and exhaustive scientific scrutiny of OTC drugs ever undertaken by a government agency at any level anywhere in the world.

It is a mammoth project involving a large number of OTC manufacturers and many thousands of OTC drugs undertaken at a cost of many millions of dollars to the federal government and substantial additional millions to the OTC medicines industry.

Seventeen Advisory Review Panels were appointed to review the safety, effectiveness, and labeling of OTC drugs. The Panels were composed of persons in the fields of medicine and pharmacology as voting members and two non-voting liaison members representing consumers and industry. The Panels were charged with the responsibility of recommending to FDA the conditions under which OTC drugs falling within their purview are generally recognized as safe and effective and not misbranded. Those Panels compile and issue reports of up to a thousand pages in length, which contain their recommendations and which are published for public comments in an Advance Notice of Proposed Rulemaking (ANPR).

After evaluating the comments, FDA issues a formal proposal, which sets forth the agency's proposed action with respect to the various ingredients and labeling claims discussed in it. The proposal is subject to further comment, objections, and perhaps an oral hearing. Later FDA issues a Final Monograph, which sets forth FDA's position on the various ingredients and claims. There are expected to be as many as seventy Final Monographs when the Review is finished, one each for the various therapeutic categories involved (antacids, internal analgesics, etc.). By any measure the OTC Review is a thorough scientific program, and one to which FDA has devoted many thousands of man hours and many millions of dollars. During this regulatory review, the Association urges that any information or concerns about specific ingredients be directed to the FDA. The OTC Review is the appropriate scientific forum for determination of the safety and effectiveness of ingredients, doses, formulations, and labeling of OTC medicines.

To help assure that FDA decisions are based on the best available scientific evidence, the OTC medicine industry has submitted many of the 20,000 volumes of scientific data. In addition, The Proprietary Association and the industry have made presentations to several of the panels. By cooperating with the OTC Review, the industry has demonstrated considerable interest in assuring that OTCs be safe, effective, and properly labeled for use by the consumer.

III. The OTC Review of Weight Control Products

One instance in which The Proprietary Association submitted data to FDA in connection with the Review involved weight control products, many of which contain phenypropanolamine, an ingredient discussed at some length during the Subcommittee's July 21, 1983 hearing. The FDA's Advisory Review Panel on OTC Miscellaneous Internal Drug Products had found phenylpropanolamine to be both safe and effective in OTC weight control products. On July 26, 1982, the Association submitted comments (copy enclosed) agreeing with that conclusion and providing new data confirming its safety and effectiveness. On August 27, 1982 the Association submitted reply comments (copy enclosed) referencing still more data affirming the safety and/or effectiveness of phenylpropanolamine and responding to the comments of those who had raised questions about it. These two submissions of the Association constituted the most comprehensive collection of clinical data available on phenylpropanolamine, consisting of more than 60 controlled clinical studies involving more than 3,700 patients, all demonstrating the safety and/or effectiveness of phenylpropanolamine. These data, together with almost 50 years of safe use of phenylpropanolamine in this country, clearly outweigh the handful of anecdotal reports of adverse effects.

IV. OTCs and the Elderly

A 1981 survey by Louis Harris and Associates for the National Counsel on the Aging, Inc. found that 47 percent of the public 18-64 years of age believes that poor health is a very serious problem for *most* people over 65. However, only 21 percent of older Americans cited poor health as a very serious personal problem. Harris concluded that "A gap between the myth and reality of aging continues to exist . . . This is particularly true with regard to health care."[4]

The elderly have about the same problems in life as younger people. Despite the public view of a bed-ridden, house-bound older American, the evident self-perception of a majority of the elderly is one of relative health and mobility. Researchers Linn and Linn concluded ". . . age, by itself, is a poor indicator of health among the elderly . . . .[5] Aging, indeed, is often a highly personal affair; a 75-year-old man may be physiologically younger than a 55-year-old male.[6]

Elderly individuals appear to use nonprescription medicines much the same as do younger individuals -- either as a response to the appearance of symptoms or signs of illness or injury, or as a means of monitoring health or preventing the occurrence of symptoms. Available evidence shows that the elderly population's use of OTCs is directly and appropriately related to their symptoms.[7]

The number of different OTCs taken by the elderly does not appear to differ from the number used by the adult population as a whole. Both seniors and the general population use OTCs at approximately the same rate.[8] A series of studies indicates that the average number of these medicines taken by older people ranges from 1.5 to 2.0 in periods of two days to two weeks, rising to perhaps 3.5 in the course of a year.[9,10,11,12] The average number of OTCs used by the elderly does not differ perceptibly from that reported for the total population, i.e., 1.5 in two days to 2.0 to 2.2 in two weeks.[13] Knapp and Knapp offered the following: "It is often assumed that (OTC) use is high, since older people suffer more afflictions than younger persons. However, two previous studies do not confirm this; they indicate that a smaller proportion of the elderly reported using nonprescribed products than do younger people. Since reasonably valid data indicate that prescribed drug use is three times as high in persons over 65 as in those under 65, perhaps the elderly treat their larger number of afflictions with more potent prescribed drug products . . . ."[14]

IV. Conclusion

Aging is a phenomenon unique to each individual. The elderlys' health demands are fashioned by specific conditions. As a result, the elderly tend to use OTCs in approximately the same fashion and in the same quantity as the general population. FDA is currently reviewing the safety, effectiveness, and labeling of all OTCs in the OTC Review. This is the most complete scientific scrutiny of OTC drugs ever conducted. Scientific evidence about specific ingredients should be submitted to the FDA for their deliberation in a scientific forum.

Sincerely,

THE PROPRIETARY ASSOCIATION

Daniel F. O'Keefe

Daniel F. O'Keefe, Jr.
Senior Vice President, General Counsel
and Secretary

DO'K/bl
8/17/83

Enclosures:

PA Comments on FDA OTC Drug Review Advance Notice of Proposed Rulemaking on Weight Control Products (July 26, 1982)

PA Reply Comments on FDA OTC Drug Review Advance Notice of Proposed Rulemaking on Weight Control Products (August 27, 1982)

REFERENCES

1 Statement of Arthur Hull Hayes, Jr., M.D., Commissioner of Foods and Drugs, to The Proprietary Association, May 11, 1981.

2 U.S. Department of Commerce, U.S. Industrial Outlook (Washington: U.S. Government Printing Office, 1978), p. 131.

3 35th Annual Report on Consumer Spending, Drug Topics, July 4, 1983.

4 Louis Harris and Associates, Inc., "Aging in the Eighties: America in Transition," a survey conducted for the National Counsel on the Aging, Inc., Nov. 1981.

5 Bernard S. Linn and Margaret W. Linn, "Objective and Self-Assessed Health in the Old and Very Old," Social Science and Medicine 14-A (1980):311.

6 University of Kansas School of Pharmacy, "Effect of Aging on Drug Action, V," continuing education by correspondence (1978).

7 R.V.H. Jones, "Self-Medication in a Small Community," Journal of the Royal College of General Practitioners 26 (1976):410-13.

8 U.S. Department of Commerce, p. 131.

9 A.E. Courtney et al., "Investigation of Use and Reasons for Use of Nonprescription Drugs: Report D: National Purchase Diary," report prepared for Canadian Department of Health and Welfare (1974), p. 3.5.

10 Robert Kohn and Kerr L. White, eds., Health Care: An International Study: Report of the World Health Organization/International Collaborative Study of Medical Care Utilization (London: Oxford University Press, 1976), p. 243.

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THE PROPRIETARY ASSOCIATION
1700 Pennsylvania Avenue N.W./Washington, D.C. 20006/Phone (202) 393-1700

July 26, 1982

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs
Dockets Management Branch (HFA-305)
Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Weight Control Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Advance Notice of Proposed Rulemaking, 47 Fed. Reg. 8466 et seq. (February 26, 1982), Docket No. 81N-0022

Dear Sir:

The February 26, 1982 Federal Register contained the above proposal, which consists of a Report and Proposed Monograph of the Advisory Panel on OTC Miscellaneous Internal Drug Products, convened by the Food and Drug Administration under its OTC Drug Review. Interested persons were invited to submit written comments by July 26, 1982.

These comments are filed on behalf of The Proprietary Association, a 101-year-old trade association, the active members of which are engaged in the manufacture and distribution of nonprescription or over-the-counter medicinal products. Members of the Association are subject to the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301, et seq.) and are interested in and affected by this proposal.

These comments are not intended to supersede any comments that may be filed by individual members of the Association.

General Comments

1. Legal Status of Monographs

The Association notes its continuing position that Monographs issued under the OTC Drug Review are interpretive, as opposed to substantive, regulations. As to this point, the Association herein incorporates by reference: (a) its comments, dated March 4, 1972, on the Proposed Procedures for Classification of Over-The-Counter Drugs; and (b) its comments, dated June 4, 1972, on the Proposed Antacid Monograph.

2. Exclusivity Policy

The Association also notes its continuing position that FDA lacks the statutory authority to prescribe exclusive lists of terms from which indications for use for OTCs must be drawn and to prohibit labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer.

The Fair Packaging and Labeling Act (15 U.S.C. 1453(a)) requires that an item bear a statement of identity. Section 502(e) of the Food, Drug and Cosmetic Act requires that the label of a drug bear the established name of the drug and, if there be none, the common or usual name. As applied to nonprescription drugs, these requirements are codified in 21 C.F.R. 201.61, which cites both acts as its authority for requiring a "statement of identity" on the principal display panel. Section 508 of the Act authorizes the Secretary to establish official names for drug substances.

None of these statutory provisions reveal any Congressional intent to grant FDA the authority to legislate the exact wording of OTC labeling, such as indications for use, and prohibit truthful labeling terms. Indeed, if manufacturers use some of the terms being prescribed by some OTC Review Panels, their labeling may well be in violation of Sec. 502(c) of the Food, Drug, and Cosmetic Act, which requires that label information be in such terms as to render it likely to be read and understood by consumers under ordinary conditions of purchase and use.

3. Inactive Ingredient Listing

The Association disagrees with the Panel's recommendation (page 8473, third column) that inactive ingredients be listed on the label. First, the listing of inactive ingredients would be meaningless to all but a handful of consumers. Second, it may overstress the importance of such ingredients and obscure far more meaningful information, such as directions for use, warnings, and even the active ingredients. Third, it may confuse consumers. Products which are similar in their purpose and even in the number and identity of active ingredients may differ widely in the number and identity of inactive ingredients. It is perhaps for these reasons that current law does not require that inactive ingredients be listed, as FDA noted in paragraph 75 of the Final Order accompanying the Antacid Monograph [39 F.R. 19862, 19871 (June 4, 1974)].

Specific Comments

1. The Proprietary Association supports the Advisory Panel's classification of phenylpropanolamine hydrochloride as generally recognized as safe and effective for appetite suppression and weight control. The Association's recommendation is based not only on the clinical evidence submitted to the Panel but also on the even more extensive clinical data which has become available since the Panel completed its Report.

The Association supports the Panel's recommendations as to both the safety and the effectiveness of phenylpropanolamine hydrochloride (PPA) for weight control.

The FDA, in its preamble to the Panel's monograph, raised specific safety questions with regard to weight control products and requested further information. At the same time the agency stated that it did not find it necessary to take action to remove from the market products at dosage levels which have a marketing history of use in OTC weight control drug products. The maximum daily dosage levels in these marketed products are an immediate-release dose of up to 37.5 mg and a timed-release daily dose of up to 75 mg phenylpropanolamine, with the total daily dose not to exceed 75 mg in either case [page 8465, second column].

The following comments seek to answer the agency's safety questions by providing the requested information, much of which relates to products not before this Panel or was not available in time for consideration by the Panel, which concluded its work on March 2, 1979.

In its preamble, the agency has raised the following questions:

a. To what extent may phenylpropanolamine hydrochloride induce hypertension in normotensive patients at the recommended dose levels?

b. To what extent may phenylpropanolamine hydrochloride aggravate pre-existing hypertension at the recommended dose levels?

c. To what extent may phenylpropanolamine hydrochloride interact with aspirin and other medications that inhibit prostaglandin synthesis at the recommended dose levels?

These questions are addressed below.

a. To what extent may phenylpropanolamine hydrochloride induce hypertension in normotensive patients at the recommended dose levels?

(1) The Panel had substantial clinical evidence that PPA does not induce hypertension in normotensive patients.

The data submitted to the Panel on safety was more than sufficient, by any standard. At least eight well-controlled clinical studies were submitted to the Panel, each of which substantiated the safety of PPA as an anorexiant. These numerous supportive studies far exceed the usual requirement of two well-controlled clinical studies. These studies are further buttressed by safe consumer use for almost half a century.

Exhibit 1 contains brief abstracts of eight of the safety and efficacy studies made available to the Panel.

(2) The safety reports referred to in the preamble, which were made available after the Panel's report was submitted, should not alter this conclusion.

Nine reports were cited in the preamble as having been made available after the Panel's report was submitted. Two of these re-confirmed the results of the studies considered by the Panel that PPA does not induce hypertension in normotensive patients. These two positive reports are the study by Silverman, et al. [Ref. 7] and the studies of 50 mg immediate and sustained release dosages by Cuthbert, Greenberg, and Morley [Ref. 6].

Of the remaining seven reports cited in the preamble, six included isolated cases of individual adverse reactions. These were the case reports of Horowitz, et al. [the portion of Ref. 2 relating to the one 17-year-old woman]; Frewein, Leonello, and Frewin [Ref.3]; King [Ref. 4]; Peterson and Vasquez [Ref. 5]; Lee, Beilin, and Vandongen [Ref.8]; and Deitz [Ref. 9]. In none of these cases was there any possibility of verification of the actual dose of phenylpropanolamine taken since the dose was reported by the patient and not taken under controlled conditions. In at least two of the cases overdoses were stated to have been taken [Ref. 2. relating to the 17-year-old-woman; Ref. 4]. In five of the seven cases, "Trimolets," an 85 mg anorexiant marketed only in Australia, was used. In only two of the seven cases was there any follow-up to determine whether the symptoms reported were repeated under the same or different circumstances. Six of the cases were simply anecdotal in nature. Clearly, any drug, OTC or prescription, has the capacity to cause idiosyncratic reactions in a small number of individual patients.

Only two of the seven adverse reports cited in the preamble were purportedly of controlled clinical studies, both conducted by Horowitz, et al. [Refs. 1 and 2]. To the first of these the agency attributes "the most striking new finding" regarding elevation of blood pressure [page 8466, second column]. However, both of these studies are inappropriate to the agency's safety evaluation of the recommended dose in the United States because the adverse reactions reported by Dr. Horowotz were the result of testing the 85 mg Australian product "Trimolets." This product was labeled as timed-release, but it is open to question whether it did in fact contain a timed-ralease mechanism. H. I. Silverman, whose study was cited in the preamble [Ref. 7], received and analyzed a small number of "Trimolets." As he has since reported to FDA, Silverman found that the PPA in the product was immediately soluble in water and was not in a sustained release form. (See Exhibit 2, p. 2.)

Silverman's analysis indicates that "Trimolets," which had been used in most of the instances of reported adverse blood pressure effects, delivered in a bolus dose approximately two-and-a-half times the maximum permitted immediate release dose (37.5 mg). The reported adverse reactions therefore were due to overdose.

(3) Finally, there is now overwhelming additional evidence from controlled clinical studies that PPA does not cause hypertension in normotensive patients.

Additional studies, six published and 41 unpublished, which were not submitted to the Panel or referred to in the preamble, support this conclusion. More than 3200 patients were included in these studies, which were not submitted to the Panel because they became available after the Panel completed its work or were conducted on PPA used as a nasal decongestant. However, the dosage levels of PPA in the nasal decongestant studies were comparable to the dosage levels of PPA in weight control products. The published studies include the following:

W. E. Barrett, et al., reporting in Current Therapeutic Research 30: 640-654, November 1981, on a bioavailability study including 18 volunteers, found no adverse effects on vital signs, blood pressure, or ECG, after giving 75 mg sustained action and 25 mg immediate release dosage forms of PPA.

Silverman, et al., reporting in Current Therapeutic Research 28: 185-94, August 1980, found no significant changes in either blood pressure or pulse values after oral administration of 25 mg phenylpropanolamine (od), with and without caffeine, in 37 volunteers.

R.E. Noble, writing in Lancet, June 19, 1982, described three large studies conducted in the past two years on more than 400 obese patients. (See Exhibit 3.) Dr. Noble wrote:

> "Data were gathered on a twelve-week, double-blind, placebo controlled study of 50 mg PPA three times daily...; a double-blind placebo controlled study of 50 mg PPA combined with 200 mg caffeine in controlled-release form; and a single-blind trial of 75 mg PPA in controlled-release form.
>
> "All three dosages caused no significant increase in blood pressure in more than 400 patients. 2 patients experienced noteworthy rises in blood pressure after treatment with 75 mg PPA, but these increases were felt not to be drug related.

> "The mean pooled systolic and diastolic blood pressure in the 50mgx3 PPA/placebo study are shown in the figure.
>
> "Our results confirm that PPA does not cause a significant increase in blood pressure even when the amount ingested (150 mg/day) is substantially higher than the 75 mg dose. There was, on the contrary, a reduction in blood pressure as the studies progressed."

J.H. Black, writing on "The control of allergic manifestations: By phenylpropanolamine (propadrine) hydrochloride" in Lancet 54: 101-102, 1937, reported no blood pressure changes or insomnia in 41 normotensive patients given 48 mg doses of phenylpropanolamine as frequently as every three hours. None of five patients who received 384 mg within two days showed greater blood pressure changes than 10 mmHg systolic. In one hypertensive patient, a 24 mg dose was associated with a decrease in systolic blood pressure, from 170 to 160 mmHg, with no change in diastolic pressure.

W.E. Boyer, reporting on "The clinical use of phenylpropanolamine hydrochloride (propadrine) in the treatment of allergic conditions" in J. Allergy 9: 509-513, 1938, stated that he administered 48 mg doses of phenylpropanolamine every two hours for five days or more with no effects on blood pressure.

C.A. Mitchell, writing on "Possible cardiovascular effect of phenylpropanolamine and belladonna alkaloids" in Ther. Res. 10: 47-53, 1968, reported no pressor effects after giving 50 mg doses of phenylpropanolamine twice daily in 32 normotensive subjects.

The as-yet-unpublished studies which demonstrate that PPA does not induce hypertension in normotensive patients are as follows:

In an eight week, double-blind, randomized study conducted by Rudolph Noble, M.D., Ph.D., in San Francisco, CA, 60 patients were divided into two groups. Thirty patients were given 75 mg of phenylpropanolamine and 200 mg caffeine, timed-release (od), and thirty patients were given 75 mg diethylpropion, timed-release. There was no significant difference in weight loss between the groups.

No significant changes in either blood pressure or pulse measurements were indicated during the test periods in comparison with the baseline measurements.

Marianne Sebok, M.D., Staff Physician at JFK Memorial Hospital, Philadelphia, PA, conducted a six-week, double-blind clinical study of 78 patients who were given either a sustained release capsule containing 50 mg phenylpropanolamine and multivitamins or placebo. The study demonstrated statistically significant weight loss for the active medication group at all measurement intervals. No clinically significant deviations were noted in blood pressure (systolic, diastolic) and pulse and there were no significant side effects.

Stanley L. Altschuler, M.D., Medical College of Pennsylvania, conducted a double-blind, 6-week clinical study of 64 patients who were given either four phenylpropanolamine drops (25 mg) or placebo drops (tid). This study demonstrated statistically significant weight loss at Week 6 for the phenylpropanolamine compared to placebo at the .04 level of confidence. No clinically significant deviations in blood pressure (systolic, diastolic) and pulse were noted, nor were any significant side effects reported.

Hoebel, Krosnick, et al., Department of Psychology, Princeton University, conducted a double-blind, crossover study in which 6 patients took a sustained release 75 mg phenylpropanolamine dose twice daily or placebo capsules. Experimental and placebo groups were reversed after two weeks so that the patients served as their own control. Body weight, pulse, blood pressure and fasting blood glucose levels were recorded three times weekly. There was no significant change in either blood pressure or pulse rate during the 4-week study in which the pre-diabetic patients received twice the daily recommended dose of phenylpropanolamine. The patients' signs were monitored in 12 separate office visits during the period of the clinical evaluation.

In a bioequivalence study at the Massachusetts College of Pharmacy and Allied Health Sciences, 75 mg phenylpropanolamine (od, SR) was compared to 25 mg (tid, IR) in 18 volunteers. No significant blood pressure effects were reported.

In a study of 125 male and female patients by Alvin P. Wenger, M.D., tablets containing 50 mg PPA (SR), 25 mg pyrilamine maleate, and 25 mg pheniramine maleate were compared with placebo for effectiveness as a nasal decongestant. Eighty patients, including all the placebo patients, were double blinded. Blood pressure evaluations were taken at two and four hours after dosage. Overall, there was no major change in blood pressure at the 95% level of confidence. The major side effect reported was drowsiness, with 56% of the PPA patients reporting at least some drowsiness and 38% of the placebo patients. (OTC Volume 040-151)

The following information was provided to the Association by a member company. It is our understanding that the company is submitting this information to FDA in greater detail.

Between 1971 and 1975, blood pressure determinations were recorded in seven studies of healthy adult volunteers to evaluate the bio-availability of PPA from various formulations. Generally, the studies were conducted as crossover trials comparing sustained-release (SR) and immediate-release (IR) formulations administered as single doses. A total of 76 volunteers were included in the studies, and they were administered 211 test doses of PPA. Blood pressure and pulse rate were determined before and on several occasions after administration of each test dose. The following test doses were administered:

> 150 mg IR doses were administered to 35 volunteers on a single occasion during three studies (#2,3,4) (12 received 150 mg as a single dose and 23 received 150 mg in divided doses over 8 hours);
>
> 150 mg SR doses were administered to 48 volunteers on 60 occasions during four studies (#2,3,4,5);
>
> 100 mg IR doses were administered to four volunteers on a single occasion during one study (#4);
>
> 75 mg IR doses were administered to 48 volunteers on 60 occasions during four studies (#1,2,4,5);
>
> 75 mg SR doses were administered to 12 volunteers on a single occasion during one study (#1);
>
> 50 mg IR doses were administered to 12 volunteers on a single occasion during one study (#3);
>
> 36 mg IR doses were administered to 12 volunteers on 24 occasions during one study (#7).

Clinically significant increases in blood pressure were detected only following administration of 150 mg immediate release PPA, and only in five out of the 35 test doses. Even in the five cases the increases were transient and blood pressure returned to baseline levels during the observation periods without medical intervention. The increases also amounted to only 10 to 30 mmHg, with the maximum reading of 100 mmHg diastolic.

Ten investigators submitted reports on a total of 337 adults and 61 children (age 12 or under) taking sustained release cough/cold capsules containing 50 mg PPA, 4 mg chlorpheniramine maleate (CPM), and 0.25 mg belladonna alkaloids. Side effects were reported in 24 (7 percent) of adult patients, including drowsiness (11 patients), urinary retention (1 patient), and nausea (1 patient). There were no reports of elevated blood pressure. No side effects were reported among the children treated.

Two hundred fifty patients were given the same 50 mg product. Side effects were reported by 54 of these patients. There were no reports of elevated blood pressure.

One hundred fifty-six patients were given the 50 mg product. Side effects reported were: dry mouth (1); headache (1); and drowsiness (2). Medication was not discontinued in any of these patients because of side effects. There were no reports of elevated blood pressure.

Twenty patients were given the 50 mg product. Side effects included: drowsiness (1); increased eye itching and congestion (1); "burnt taste in stomach" (1); nosebleed (1). Medication was not discontinued in any of these patients. There were no reports of elevated blood pressure.

In a comparative study of this product and a product containing APAP 195 mg, pyrilamine maleate 25 mg, caffeine 15 mg, ephedrine sulfate 8 mg, and phenylpropanolamine hydrochloride 25 mg, 25 patients took the 50 mg PPA product and 23 took the 25 mg PPA product. Side effects were noted. There were no reports of elevated blood pressure.

One hundred eighty-eight patients were given twice daily sustained release cough/cold capsules containing 50 mg PPA, 4 mg CPM, and 0.25 mg belladonna alkaloids. Side effects were observed in 13 of the patients studied. Dryness of mouth - a reaction to the belladonnas - was reported by five patients. Upset stomach occurred in a patient being treated for ulcer symptoms. Two patients reported "jitteriness" and "irritability" and had the drug discontinued. One case of urinary retention developed in an elderly male (age 72). There were no reports of elevated blood pressure.

In another study, 111 patients were given the same 50 mg product twice daily. Dry mouth was noted in two of the patients. No other adverse effects were noted.

Eighty patients were given the same product twice daily for a period of two to six days. Side effects noted were: drowsiness (10); dry mouth (4); urinary retention (1); and nausea (1). There were no reports of elevated blood pressure.

Eighty-four patients were given the same product twice daily for one to 14 days. There was one report of dry mouth and no reports of elevated blood pressure.

Thirty-six patients took the same product. No side effects were reported.

Eighty-eight patients were given the same product twice daily. There were no adverse effects noted.

Fifteen normal volunteers received the same product for a period of six months. Pre-drug data were collected two weeks prior to dosing and one week prior to dosing. Dosage was one capsule twice daily. Two volunteers did not complete the study, for non-medical reasons. There was no control group. Results of this study showed that the product was safe for long-term use. Side effects noted were: blurring of vision (1) and abnormal SGOT, probably due to low-grade hepatitis (1). Diastolic blood pressure averages remained uniform throughout the study. Systolic blood pressure averages showed a slight increase (at Weeks 12, 13 and 20), though the mean systolic pressure was 125.5 mmHg. At Week 28, mean blood pressure was 120.5/75 mmHg. Pulse rate dropped early in the study, although this decrease did not coincide with the systolic blood pressure change. It was felt that all of the changes seen could be related to the volunteers' activities during different phases of the study.

In a three-year study evaluating the same 50 mg product versus placebo, 450 patients participated. Of the patients taking the medication, 11.5 percent developed possible side effects. Of the patients taking placebo, 8.2 percent experienced possible adverse effects. There were, however, no reports of elevated blood pressure.

A double-blind study of 178 patients with symptoms of acute coryza was undertaken comparing the effects of a product containing phenylpropanolamine HCl 75 mg and chlorpheniramine maleate 8 mg, in a sustained-release capsule; a sustained release product containing PPA 50 mg, CPM 4 mg, and belladonna alkaloids 0.25 mg; and placebo. Adverse reactions were reported by 10 percent of the patients taking the 75 mg PPA product, 12 percent taking the 50 mg PPA product, and 9 percent taking placebo. There were no reports of elevated blood pressure.

L.B. Cobin reported that mean blood pressure and pulse rates were not affected by 50 mg SR PPA (bid), 0.2 mg belladonna alkaloids (bid), a combination of the above, or placebo in 20 normal volunteers.

Dr. Richard Mulberger found no reports of elevated blood pressure during a crossover study on the comparison of placebo and a sustained release product containing PPA 50 mg, CPM 4 mg, and belladonna alkaloids 0.25 mg on intraocular pressure in normal glaucoma patients.

J. Colemore conducted an open study using 10 volunteers who received 75 mg PPA (bid, SA) for 8 weeks. No clinically significant blood pressure or pulse effects were seen. (NDA 12-685, OTC Vol. 040012.)

H. Maibach conducted an open study using 15 volunteers who received 50 mg PPA (bid, SA) for 6 months. No clinically significant changes were seen in blood pressure or pulse values. Slight increases in systolic blood pressure were seen in Weeks 12, 13, 18 and 19. (NDA 12-685, OTC Vol 040012.)

An open, crossover bioavailability study of 150 mg phenylpropanolamine (od, SA), 75 mg phenylpropanolamine (od, IR), and 50 mg phenylpropanolamine (od, IR) was conducted, using 12 volunteers. No significant blood pressure effects were recorded. (NDA 18-099.)

b. To what extent may PPA aggravate pre-existing hypertension at the recommended dose levels?

Clinical studies demonstrate that PPA does not aggravate pre-existing hypertension.

Two clinical studies have come to this conclusion, one published and one unpublished. D.L. Unger, L. Unger and D.E. Temple reported on the "Effect of an anti-asthmatic compound on blood pressure of hypertensive asthmatic patients" in Ann. Allergy 25: 260-261, 1967. Doses of 25 mg phenylpropanolamine were given three times a day to 21 asthmatic hypertensive patients for one to three weeks. Baseline blood pressure averaged 166/102; within one hour after admnistration, the average blood pressure was 164/102. The median blood pressure pre-dosing was 164/104 and after dosing 168/102. Five patients had a 10 mmHg elevation in systolic blood pressure and five had a decrease of 10 mmHg. Four patients had a 10 mmHg elevation and four a 10 mmHg decrease in diastolic blood pressure. None of the patients studied had to discontinue use of phenylpropanolamine because of side effects. The authors concluded that phenylpropanolamine produced no significant changes in blood pressure at the time of peak blood levels following administration of 25 mg doses.

In a pilot, single-blind, crossover study conducted by M.H. Bradley, M.D., on ten exogenous obese patients with controlled hypertension, no clinically significant changes in blood pressure values were seen in patients who were given 25 mg PPA (tid), placebo, and 75 mg PPA (od). (See Exhibit 4.)

c. To what extent may PPA interact with aspirin and other medications that inhibit prostaglandin synthesis at the recommended dose levels?

There is abundant evidence from the long use of PPA/aspirin combinations in OTC cough/cold products that such combinations do not induce hypertension. This has been confirmed conclusively by clinical studies of aspirin alone and of aspirin in combination with phenylpropanolamine.

The agency's request for information on this question arises from a report on a single patient. Lee, Beilin, & Vandongen [Ref. 8] reported severe hypertension in a single patient taking an 85 mg dose of phenylpropanolamine together with a 25 mg dose of the non-steroidal anti-inflammatory medication, indomethacin, although neither of the drugs was associated with hypertension in the patient when given alone. The authors of this single patient report apparently postulated that the decrease in prostaglandin levels due to indomethacin concomitantly reduced the inhibitory action on catecholamine release. As a result, the administration of phenylpropanolamine may have invoked a greater than expected release of catecholamines, resulting in profound vasoconstriction and an increase in blood pressure.

The record indicates that hypertension is known to occur from the clinical use of indomethacin (A. Wennmalm, "Influence of Indomethacin on the Systematic and Pulmonary Vascular Resistance in Man," Clin. Sci. Mod. Med. 54: 141-145, 1978; 1982 Physicians Desk Reference). However, no such data is available with regard to aspirin. Furthermore, the known long-term concurrent use by patients of aspirin and phenylpropanolamine to alleviate the discomfort of the common cold has not indicated evidence of any significant hypertensive responses.

There have been several large, well-controlled studies which have examined the potential for chronically administered aspirin to influence blood pressure. No hypertensive effect of aspirin has ever been demonstrated (The Coronary Drug Project Research Group, "Aspirin in Coronary Heart Disease," J. Chron. Dis. 29: 625-642, 1976; A.A. Cooper, "Efficacy of Zomepirac in Oral Surgical Pain," J. Clin. Pharmacol. 20: 230-242, 1980).

There are a number of leading non-prescription cold and allergy products which have combined aspirin with phenylpropanolamine in addition to other ingredients (Handbook of Nonprescription Drugs, Sixth Edition, Amer. Pharm. Assoc., Washington, D.C. 1979, pp. 107-112). Many nonprescription and prescription combination products have been used safely for many years in the United States as well as in Europe. If there were any real potential for interaction between aspirin and phenylpropanolamine or any other sympathomimetic, it would certainly have been obvious. Yet the market experience has been remarkably free of adverse reactions. A consortium of cough/cold product manufacturers made a presentation to the Cough/Cold Panel on September 1, 1974, in which they submitted the following data on adverse reactions per 100,000 packages of various leading combination products:

Combination	Adverse Reactions Per 100,000	Total Packages Sold
PPA and acetaminophen	0.282	1 million to 10 million
PPA, chlorpheniramine, and aspirin	0.109	10 million to 50 million
PPA, chlorpheniramine and calcium carbaspirin	0.091	1 million to 10 million

This admirable record of reported adverse reactions over the years of use of these products indicates how remote is the possibility of significant occurrence of the adverse reaction in question.

Clinical evidence that a therapeutic interaction between aspirin and PPA does not occur is well demonstrated in a 30-day human study. (Cough, Cold, Asthma, Bronchodilator and Allergy Panel Report, F.R. Sept. 9, 1976; OTC Volume 040293 (1971)). This double-blind, clinical trial employed a total patient population of 68 (65 male; 3 female), and included four identical-appearing tablets of different composition provided to subjects by random assignment. Dosage was two tablets taken 4 times daily.

Formula Code	Composition per tablet	Total Daily Dose
SHP-78	ASA-325 mg PPA- 25 mg	2600 mg 200 mg
SHP-79	PPA- 25 mg	200 mg
SHP-80	ASA-325 mg	2600 mg
SHP-82	Placebo	

A total of 26 patients completed 30 days on the complete regimen using SHP-78 while three other groups of nine patients per group completed the 30-day therapy using the other three dosage forms. Subjects not consuming the assigned dosages were dropped from the study.

Formula Code	SHP-78	SHP-79	SHP-80	SHP-82
Subjects Assigned	34	11	11	12
Subjects Dropped	8	2	2	3
Subjects Completed	26	9	9	9

All subjects were provided with clinical and laboratory evaluations including blood chemistry, urinalysis, blood count, blood pressure, pulse rates, body weights, and oral temperatures. Pulse and blood pressure were monitored on Days 0 (day prior to administration), 7, 15, 22 and 30. One patient in the ASA group exhibited a dramatic increase in pulse rate on Day 30. This was attributed to personal problems on that day specifically and was not considered to be drug-related. The conclusion reached upon completion of the study was that no evidence of drug-related toxicity was observed or determined.

This study therefore provides conclusive evidence of a lack of interaction between PPA and aspirin. Additionally, it provides further support for the proposition that PPA does not adversely affect blood pressure. Subjects in this study ingested a total of 200 mg PPA daily for 30 days in individual 50 mg doses. Tablets were not sustained release. A total of 35 subjects completed the 30-day regimen taking PPA. On the basis of the dosage employed, the number of subjects enrolled, and the length of time they received a combination of PPA with the non-steroidal anti-inflamatory product aspirin, no adverse effects relative to blood pressure or other vital signs were reported.

Summary

The data that was before the Panel, and the more extensive data which has become available since the Panel completed its work, constitutes a massive amount of scientific evidence drawn from 60 controlled clinical studies involving more than 3,700 patients. This data demonstrates that PPA does not induce hypertension either in normotensives or hypertensives or when it is in combination with aspirin. This data, together with almost 50 years of safe use of PPA in this country, clearly outweighs the handful of adverse reports referred to in the agency's Preamble.

2. The Proprietary Association recommends that the FDA accept the Panel's recommendation with regard to labeling for the combination of phenylpropanolamine hydrochloride and caffeine.

The Panel Report recommends Category I status for the combination of phenylpropanolamine hydrochloride and caffeine if labeled as an "Anorectic/Stimulant" (page 8476, first column). In its preamble FDA invites comment on alternate or consolidated label warnings and directions for such combinations, noting that a discrepancy exists between the directions for use of caffeine in this and another current proposal to the agency (page 8469, first column).

The warning proposed in the Tentative Final Monograph of the Panel on Over-The-Counter Nighttime Sleep-Aid and Stimulant Products (Sleep-Aid Panel) was, "For occasional use only." (§ 340.50(c)(2); 43 F.R. 25602). However, the warning proposed by the Miscellaneous Internal Panel for Weight Control Products specified daily doses for up to three months. (§ 357.550(d); page 8484, second column).

We do not believe the agency's concern about this discrepancy is warranted. Caffeine in combination with phenylpropanolamine hydrochloride in weight control products is intended only as adjunctive therapy, used to mitigate the lethargy that may accompany a reduced diet regimen. As the Panel Report stated,

> ". . . the Panel had to decide whether or not a significant portion of the dieting population becomes fatigued while dieting. Based upon its professional experience the Panel concluded that such a significant patient population does exist and that the combination of phenylpropanolamine hydrochloride and caffeine meets the three criteria of FDA's combination policy." (Page 8476, first and second columns).

By contrast, caffeine in stimulant products is intended to "help restore mental alertness or wakefulness during fatigue or drowsiness" whenever these conditions occur. (§ 340.3; 43 F.R. 25602).

In addition, the quantity of caffeine in the weight control products is inherently limited to 600 mg per day by the current and recommended maximum frequency of dosage of three times a day. Again, by contrast, when caffeine is used as a stimulant product, the recommended maximum dosage can be as much as 1200 mg per day (100 to 200 mg not more often than every 3 to 4 hours).

Therefore, it is appropriate to require the more restrictive warning on the caffeine products for relief of general fatigue and drowsiness.

Moreover, the amount of caffeine involved in combination with phenylpropanolamine hydrochloride in the weight control products is 100 to 200 mg. It is essential to note that this is only the equivalent of approximately two cups of coffee. In these dosages, caffeine has been found to be safe, either alone or in combination with other substances, by three other OTC advisory panel reports, in addition to the Weight Control Products Panel Report. The most recent of these other panel reports, on Orally-Administered Menstrual Drug Products, summarized all three panel reports as follows:

> "(2) Caffeine. The Panel concludes that caffeine is generally recognized as a safe and effective diuretic for OTC use in the doses noted below in relieving water accumulation symptoms of the premenstrual and menstrual perod.
>
> "(i) Safety. The toxicity of caffeine has been reviewed extensively by the Advisory Review Panel on OTC Sedative, Tranquilizer, and Sleep Aid Drug Products in a report published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). That Panel discussed, in addition, the mutagenic effects of caffeine in detail. It found caffeine to be safe ". . . when used in the recommended oral dose of 100 to 200 milligrams (mg) not more often than every 3 to 4 hours." FDA concurred with the Panel in the tentative final monograph published in the FEDERAL REGISTER of June 13, 1978 (43 FR 25544).
>
> "The Internal Analgesic Panel also reviewed caffeine for its analgesic properties in the FEDERAL REGISTER of July 8, 1977 (42 FR 35346) and expressed its agreement with the conclusions of the Advisory Review Panel on OTC Sedative, Tranquilizers and Sleep Aid Drug Products regarding the safety of caffeine. This Panel

> agrees with the above reports and concludes that caffeine is safe as an OTC diuretic for relieving water accumulation symptoms of the premenstrual and menstrual period in doses of 100 to 200 mg every three to four hours." Second Information Copy, OTC Orally Administered Menstrual Drug Products Report, September 22, 1981, pp. 55-56.

In its final meeting on October 16-17, 1981, the Panel, in its review of the Menstrual Drug Products Report, added to this conclusion its approval of a combination of caffeine with a menstrual product. Moreover, it did so based on the same rationale it used for its approval of the combination of phenylpropanolamine and caffeine in weight control products, that is, relief of fatigue. The minutes of the Panel meeting state:

> "The Panel was made aware that caffeine is contained in an OTC menstrual drug product (a combination product) which contains a claim for the relief of fatigue in the premenstrual period. Because the Panel has already recognized that fatigue is a component of the premenstrual syndrome and because caffeine has already been classified as a Category I stimulant by another panel, this Panel concludes that caffeine is an effective menstrual drug product ingredient for the claim of relieving fatigue occurring in the premenstrual period." Summary Minutes of the Forty-Sixth Meeting of the OTC Miscellaneous Internal Drug Products Panel, October 16-17, 1981, p. 5.

Finally, it is noteworthy that even in FDA's current inquiry regarding the use of caffeine as an added food ingredient, the agency has specifically exempted from that inquiry the presence of caffeine in coffee and the use of caffeine in drugs.

3. The Association disagrees with the Panel's conclusion that vitamins and minerals should not be constituents of weight control drug products.

The Panel report notes that some weight control products now on the market contain a number of vitamins and minerals in addition to their weight control active ingredients. The Panel also states its belief that it is the responsibility of the consumer "to determine the dietary regimen to follow in order to maintain a well-balanced, low-calorie diet" (page 8472, third column).

We share the Panel's belief in this regard. However, we strongly disagree with the Panel's conclusion which is purportedly based upon this belief. The Panel somehow leaps from its belief about a well-balanced diet to the conclusion that "therefore, the addition of vitamins and minerals [in combination with the weight control active ingredients] serves no useful purpose for those following a well-balanced diet" and "vitamins and minerals should not be constituents of weight control drug products" (id.).

The Panel's conclusion does not follow logically from its premise and also conflicts with one of the Panel's other recommendations, which FDA strongly endorses in the preamble, that "a reduction in total daily caloric intake below the energy output" must accompany weight control drug products in order to achieve significant weight loss (page 8468, third column; page 8469, first column; page 8472, second and third columns). Again, we agree with this recommendation.

However, a consumer who follows this label direction and reduces caloric intake below the energy output may, no matter how well-balanced the resultant diet, also reduce the amount of vitamins and minerals previously needed to maintain the consumer's body weight and frame. The recommended dietary intake of essential nutrients, particularly vitamins and minerals, may be difficult to achieve during caloric reduction, since in many foods vitamins and minerals are present only in low concentrations. Under these circumstances it may be desirable to provide the consumer with the option of obtaining a vitamin and mineral supplement in combination with phenylpropanolamine hydrochloride appetite suppressant in order to replace those vitamins and minerals lost as a result of lowering food intake.

Finally, vitamins and minerals which are dietary supplements are foods and should be treated as such in this combination. Combinations of cosmetics and drugs are permitted so long as each complies with applicable regulations. The same rule should be applied to the combination of vitamins and minerals with weight control active ingredients. The Bureau of Drugs should impose no more stringent requirements on such a vitamin and mineral supplement than does the Bureau of Foods.

It is in the best interest of good medicine and of the consumer to make generally available the greatest possible variety of safe and effective medication. Manufacturers should therefore not be prohibited, contrary to the Panel's recommendation, from offering such a rational combination of PPA and vitamins and minerals.

4. The Proprietary Association recommends that the FDA reject some of the Panel's recommendations with regard to Category II labeling.

The Association recommends that the following claims recommended by the Panel to be placed in Category II should instead be placed in Category I. We believe that some of these claims represent the same claims which the Panel recommended be placed in Category I but are stated in language that is more readily understood by the consumer. Others are truthful statements or, at most, amount to acceptable puffery. Indeed, the Panel itself stated that it "is aware that there may be other terms that would be acceptable in expressing the same Category I indications" (page 8473, first column).

These thirteen statements should not be classified in Category II because they do not, in fact, lead to use of the product other than in the manner recommended by the Panel as generally recognized as safe and effective. Each of these Category II claims is discussed below:

a. "Contains one of the most powerful diet aids available without prescription" (page 8476, second column). This is a true statement. The Panel recommended only two substances - - phenylpropanolamine hydrochloride and benzocaine - - for Category I as safe and effective.

b. "Contains one of the strongest diet aids available without prescription" (id.). Like claim "a", this is a true statement for products containing phenylpropanolamine.

c. "Encourages water loss with a gentle diuretic" (id.). This is a true statement for products containing caffeine. Caffeine has been recommended for Category I as a diuretic by the panel reviewing orally-administered menstrual drug products and in Category I as a mild stimulant by both the Nighttime Sleep-Aid and Stimulant Products Panel and the panel reviewing menstrual drug products. A fuller discussion appears above on pp. 17-19 in section 2 relating to the labeling for caffeine/phenylpropanolamine combinations.

d. "Easy-to-follow reducing plan built around food you love to eat. You will eat well but less and lose weight without going hungry" (id.). Clinical studies submitted to the Panel demonstrate weight loss where caloric intake has been reduced in accordance with diet plans recommended along with these products. These diet plans contain a wide variety of nutritious foods, limited only in quantities, not in the breadth of the array of foods specified. This labeling should certainly be allowed on products which are packaged with a diet plan.

e. "A unique way to help your overweight patient eat less" (id.). This is a true statement because these products involve the consumer's using a specific, approved medication to reduce appetite, rather than requiring the consumer to simply try to follow exhortations to reduce calories without the assistance of medication.

g. "Now enjoy a slim, trim figure. Lose pounds. Reduce inches" (page 8476, third column). These claims are lay descriptions of goal-oriented products and are helpful in encouraging proper compliance with product instructions.

h. "Lose weight starting today. Look your best, feel your best" (id.). This is a true statement. When caloric intake is reduced below energy requirements, the body begins to use up stored fat for energy. The claim does not refer to any specific amount of weight loss on the first day. While the amount may be relatively small, it is nonetheless a start and, once the process starts, the end result is closer than before. Like claim "g," these claims are lay descriptions of those goals and are helpful in assuring proper compliance with product instructions.

i. "The delightful aid to appetite control" (id.). Except for "delightful" this is the same as "An aid in the control of appetite," recommended for Category I by the Panel (page 8475, first column, ¶ 2(6)). The addition of "delightful" is harmless puffery, fully justified by the fact that the recommended diet plans enclosed with the products contain a broad array of foods. The reasoning for this is the same as for claim "d" above.

j. "Delightfully delicious, scientifically formulated to help you control your appetite quickly, pleasantly" (page 8475, second column). As in the case of claim "i", above,

CONCLUSION

The Association supports the Panel's classification of phenylpropanolamine hydrochloride as generally recognized as safe and effective when used in OTC weight control products. The extensive data discussed above demonstrate the safety of phenylpropanolamine at the 150 mg daily dosage level and amply support the safety of the currently-marketed weight control products at the 75 mg daily dosage level. The Association also supports the Panel's recommendation that the combination of phenylpropanolamine and caffeine is safe and effective if labeled as an "anorectic/stimulant."

The Association believes that weight control active ingredients in combination with vitamin and mineral supplements should be allowed, contrary to the Panel's recommendation. In addition the Association urges that FDA reject some of the Panel's recommendations with regard to Category II labeling.

The Association appreciates the opportunity to submit these comments and hopes that the agency finds them helpful.

Sincerely,

THE PROPRIETARY ASSOCIATION

James D. Cope
President

EXHIBIT 1

"Comparison of the Anorectic Activity of Prolamine and Placebo Without Concomitant Nutritionally Balanced Diet." Marianne Sebok, M.D., Staff Physician, JFK Memorial Hospital, Philadelphia, PA. A double-blind six week clinical evaluation was conducted with 72 patients who received either 35 mg phenylpropanolamine and 140 mg caffeine (sustained release) or a placebo twice a day. Throughout the study, no clinically significant variations at sitting blood pressure or pulse were observed or reported. PPA patients lost statistically significant amounts of weight compared with placebo patients.

"Double-Blind Evaluation of Phenylpropanolamine-Caffeine Product as an Adjunct in the Treatment of Obesity." E. R. Jolly, M.D., BioMetrics Laboratory, Clifton, NJ. Findings: A double-blind 12-week study of 63 patients revealed that 21 patients on phenylpropanolamine-caffeine showed an average weight loss of 15 pounds, and 13 patients on placebo showed a weight loss of 8 pounds over the 12-week test period, or 1.2 pounds per week for the phenylpropanolamine patients compared to .66 pounds per week for the placebo patients. Side effects were minimal and equally divided amoung placebo and active drug groups. One patient on the active medication reported hyperstimulation and sleeplessness and one patient on the placebo noted extreme nervousness. No significant changes in blood pressure or pulse rate were observed.

"Double-Blind Clinical Evaluation of the Anorectic Activity of Phenylpropanolamine Alone Compared to Phenylpropanolamine Plus Caffeine in the Treatment of Outpatients with Exogenous Obesity." Anthony Conte, M.D., Pittsburgh, PA. In an 8-week double-blind randomized clinical test, phenylpropanolamine 50 mg was compared to phenylpropanolamine 50 mg with caffeine 200 mg (sustained release.) Of the sixty-two obese adults who entered the clinical evaluation, both groups lost similar amounts of weight. No deviations from baseline were reported in sitting blood pressure (systolic/diastolic) or pulse.

In an open, crossover comparative study, the bioavailability of 25 mg phenylpropanolamine (q4h, IR), 75 mg (od, IR) and 75 mg (od, SA) was tested in 18 volunteers by Donald Flaster, M.D. No significant blood pressure effects were reported.

Griboff, et al., reporting in Current Therapeutic Research 17: 535-43, 1975, found no significant changes in blood pressure or pulse measurements in a double-blind parallel study on 66 volunteers receiving 25 mg PPA with 100 mg caffeine (tid) or placebo. PPA patients lost significant amounts of weight compared with placebo patients.

Altschuler, Sebok and Conte conducted 6-8 week, double-blind, parallel studies using 50 mg PPA (od, SR), 37.5 mg PPA (bid, SR), and 25 mg PPA (tid, IR), respectively. No significant effects on blood pressure or pulse rate were reported or observed. Significant weight loss was reported.

In a double-blind, crossover study conducted by Bartley G. Hoebel, Ph.D., et al., at Princeton University, Princeton, NJ, phenylpropanolamine (25 mg, tid) reduced body weight in 70 adults significantly more than a placebo pill. During the first two weeks both the subjects taking the placebo and those taking phenylpropanolamine lost weight, but during the second two weeks only those taking the drug continued to lose. On daily questionnaires those taking the drug reported no change in the way they felt or the time it took to fall asleep.

F. B. Bohensky, M.D., Brooklyn, New York, conducted a single-blind, four-week, crossover clinical evaluation of 60 patients in Dr. Bohensky's private offices. Appedrine (25 mg phenylpropanolamine plus 100 mg caffeine plus multivitamins, tid) was compared to dextro-amphetamine and placebo as an appetitie suppressant. The results indicated that the phenylpropanolamine group (Appedrine) on the average lost 1.98 pounds per week, the dextro-amphetamine group on the average lost 2.3 pounds per week, and the placebo group on the average lost .62 pounds per week. No significant changes in blood pressure or mood changes were reported or observed.

Exhibit 2

Massachusetts College of Pharmacy
and Allied Health Sciences

September 25, 1981

J. Richard Crout, MD, Director
Bureau of Drugs, HFD-1
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Crout:

This letter is in follow-up to our discussions on sustained action dosage forms and your interest in the physiological response to a 75 mg bolus dose of phenylpropanolamine HCl. You will recall, I'm sure, our meeting on September 11th in the Commissioner's office at which time we reviewed the F.R. publication status of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products - Proposed Monograph for OTC weight control drug products.

As an avid student of the sustained action dosage form and phenylpropanolamine, I was certain, as I advised you at the meeting, that my files included descriptions of experimental work where a 75 mg bolus of PPA had been administered to human volunteers in a plain immediate release dosage form and the hemodynamic response studied. The SBA for NDA 18-099, "Contac" provides information describing a three way cross-over study employing twelve normal human volunteers. The three dosage regimens were:

(A) Two "Contac" sustained action capsules containing 75 mg PPA and 8 mg CPM per capsule.

(B) 75 mg PPA and 8 mg CPM, plain drug as a bolus dose.

(C) 50 mg PPA and 5.33 mg CPM, plain drug at 0, 4 and 8 hours.

The bioavailability study determined plasma levels at the 1, 2, 3, 4, 6, 8, 10, 12 and 24 hour periods following drug ingestion. In addition, blood pressure and pulse (supine and standing) were taken

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[illegible]

before and at 1, 5 and 11 hours after drug dosing. No clinically significant change in blood pressure or pulse in any volunteer during the study was reported. I might add this information is especially important in view of the report by Horowitz, et al "Hypertensive Responses Induced by Phenylpropanolamine in Anorectic and Decongestant Preparations", Lancet, 1980; 1:60-61. The Horowitz study would suggest one might expect an increase in supine diastolic blood pressures in some volunteers ingesting a 75 mg PPA bolus, inasmuch as the dose of PPA in the Australian study was reported to be 85 mg, only 10 mg greater. However, no clinically significant changes in blood pressure are reported in the carefully controlled study submitted in support of NDA 18-099.

At the time of our own studies, ("Lack of Side Effects from Orally Administered Phenylpropanolamine and Phenylpropanolamine with Caffeine: A Controlled Three-Phase Study", Current Therapeutic Research 28, 185-194; 1980) we received a small number of the Australian product "Trimolets" for evaluation. "Trimolets" was the 85 mg PPA product reported on in the Horowitz paper. The capsules contained a fine yellow powder labelled to contain D-phenylpropanolamine 85 mg plus ferrous gluconate, calcium pantothenate, thiamine, riboflavin, pyridoxine and nicotinamide. Only three capsules were received assaying out at 82.2 mg, 79.7 mg and 83.5 mg respectively (average 81.8 mg). The PPA in these capsules was immediately soluble in water, and not in a sustained release form.

Regarding the integrity of the sustained release dosage form marketed in this country, I would like to add that our laboratories have, for years now, evaluated hundreds of pelletized sustained release PPA dosage forms marketed by the Thompson Medical Company. Our laboratories provide a periodic quality control audit and assurance function for Thompson as a further check to insure compliance of manufactured dosage forms with product specifications. I am pleased to indicate we have never encountered a product where "dose-dumping" under in vitro testing occurred and the sustained release character of a dosage form was compromised. The number of safety and quality control steps taken, prior to batch release, assure safety and efficacy of the sustained action product and provides an exceptional degree of quality assurance ruling out any possibility of the occurrence of "dose-dumping." Clinical bioavailability studies have provided assurance of the effectiveness of the timed-release activity with excellent correlation between a single dose of the timed-release formulation (75 mg) and three doses of the immediate release dosage form (25 mg) taken at 4 hour intervals. Hence, ongoing in vitro quality control, in our experience, assures product performance on a level consistent with the in vivo results.

Thompson's 75 mg timed-release PPA dosage forms are manufactured to conform with the following in vitro dissolution pattern limits.

Hour	% Release	mg Release
1	30 - 45	22.5 - 33.75
4	50 - 75	37.5 - 56.25
8	80 - 100	60 - 75

The dissolution pattern is developed by sampling at 1, 2, 4, 6 and 8 hours.

I trust these comments are a helpful sequel to our earlier discussion and provide some assistance to you.

Sincerely,

PFEIFFER PHARMACEUTICAL
SCIENCES LABORATORIES

H. I. Silverman

H.I. Silverman, D.Sc.
Professor and Executive Director

HIS/lf

cc: Mrs. Barbara Bayer
Marion J. Finkel, MD
William E. Gilbertson, Pharm.D.
Judith K. Jones, Ph.D.
Mark Novitch, MD
Dr. Edward Steinberg

of system involvement and with presentation either in childhood or in adulthood, treatment would generally be in conjunction with other specialists. Seeing patients together in combined clinics would seem to be the best way of achieving this.

There is an air of defeatism related to many lethal or seriously handicapping genetic disorders. Clinical geneticists must not encourage this by being satisfied to limit their involvement to diagnosis and genetic counselling.

Royal Manchester Children's Hospital,
Manchester M27 1FG
M. Super

PHENYLPROPANOLAMINE AND BLOOD PRESSURE

SIR,—Although phenylpropanolamine (PPA) has been safely used in the U.S.A. for over forty years as a nasal decongestant, your April 10 editorial raised the possibility that PPA in weight control preparations could produce increased blood pressure.

In the past two years, I have done three large studies in our obesity clinic in San Francisco of the effects of three dosage forms of PPA. More than 400 obese patients were studied. The results will be published elsewhere.

Data were gathered on a twelve-week, double-blind, placebo controlled study of 50 mg PPA three times daily (twice the recommended dose for weight loss); a double-blind, placebo controlled study of 50 mg PPA combined with 200 mg caffeine in controlled-release form; and a single-blind trial of 75 mg PPA in controlled-release form.

All three dosages caused no significant increase in blood pressure in more than 400 patients. 2 patients experienced noteworthy rises in blood pressure after treatment with 75 mg PPA, but these increases were felt not to be drug related.

The mean pooled systolic and diastolic blood pressure in the 50 mg × 3 PPA/placebo study are shown in the figure.

Our results confirm that PPA does not cause a significant increase in blood pressure even when the amount ingested (150 mg/day) is substantially higher than the recommended 75 mg dose. There was, on the contrary, a reduction in blood pressure as the studies progressed.

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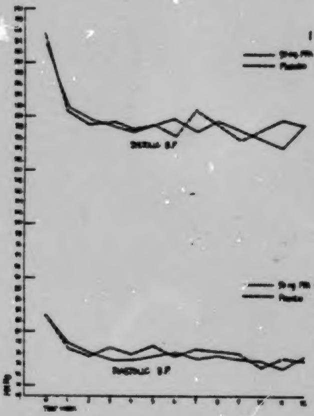
Rudolf E. Noble



Mean systolic and diastolic blood pressure.

CEFTAZIDIME AND SALMONELLA

SIR,—Dr Gozzard and colleagues (May 22, p. 1152) listed a *Salmonella newport* septicaemia treated with ceftazidime 1 g three times daily as a failure. The minimum inhibitory concentration for that strain was 0·25 μg/ml. Probably the dosage was too low. We have treated a 33-year-old African man, who had sickle cell anaemia and an osteomyelitis with *S. typhimurium* (MIC 0·25 μg/ml), successfully with, at first, 2 g twice daily for 17 days and, after an operation, 3 g twice daily for 25 days. The bone marrow sample taken during operation was sterile. A higher dosage is probably required in *Salmonella* (and, possibly, *Shigella*) infections. Of interest would be information on susceptibility of the isolated organisms to other currently available antibiotics and successful treatment of the infections by ceftazidime, where prior antibiotic therapy had failed.

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MYOCARDIAL CARNITINE DEFICIENCY IN ACUTE MYOCARDIAL INFARCTION

SIR,—Dr Suzuki and colleagues (Jan. 9, p. 116) reported decreased levels of free L-carnitine in the myocardium of chronic heart failure patients and a concomitant rise in acylcarnitine. These changes are related to a removal of accumulated free fatty acid (FFA) and long-chain acyl-CoA esters secondary to chronic hypoxia which in turn inhibits adenine nucleotide translocase.[1] This metabolic device, also observed in dog hearts during the reversible phase of ischaemia[2] seems to act as a servo mechanism tending to relieve myocardial injury. Suzuki et al. suggested the administration of exogenous L-carnitine during acute and chronic cardiac ischaemia. In acute experimental ischaemia, however, progressively more total L-carnitine is lost the longer the ischaemia lasts.[2] The two findings strongly suggest that the maintenance of physiological levels of L-carnitine and the acylcarnitine to free carnitine ratio play an important role in the control of the metabolism of the injured myocardium.

We measured[3,4] heart L-carnitine levels at necropsy in seven patients who had had acute myocardial infarctions and in four who had died from causes other than heart disease. In the first group the tissue samples were removed from the necrotic area, from the border zone, and from the healthy myocardium; whereas in the controls L-carnitine levels were separately determined in specimens taken from the left ventricular walls. The necrotic myocardial areas had lower L-carnitine levels, while the border zone tissue showed intermediate values between necrotic and healthy surrounding tissue levels. There was no discrepancy between the myocardial L-carnitine values in the controls and those found in the healthy surrounding tissue of those who had died from myocardial infarction.

We did not observe short and long chain carnitine esters in the tissue fragments of either group, presumably because in specimens removed 24 h after death all the L-carnitine content is present in the free isomer form, as a result of hydrolysis during the period since death and during storage at −25°C for 10–15 days. Therefore, in our experimental model free L-carnitine corresponds to total carnitine. This statement is supported by the fact that the tissue L-carnitine levels we found in the healthy myocardium were identical to the total L-carnitine levels measured by Cederblad in the myocardium of heart surgery patients.[5]

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1. Shug AL, Shrago E, Bittar N, Folts JD, Koke JR. Acyl-CoA inhibition of adenine nucleotide translocation in ischemic myocardium. *Am J Physiol* 1975; 228: 689.
2. Shug AL. *Changes in tissue levels of carnitine and other metabolites during myocardial ischemia and anoxia. Arch Biochem Biophys* 1978; 187: 25.
3. Pearson DJ, Tubbs PK, Chase JFA. Carnitine and acetyl carnitine. In: Bergmeyer HU, ed. *Methods of enzymatic analysis*: Vol IV. New York: Academic Press, 1974: 1758.
4. Seccombe DW, Dodek P, Frohlich J, Hahn P, Skala JP, Campbell DJ. Automated method for L-carnitine determination. *Clin Chem* 1976; 22: 1589.
5. Cederblad G, Lindstedt S, Lundholm K. Concentration of carnitine in human muscle tissue. *Clin Chim Acta* 1974; 53: 311.

Exhibit 4

THOMPSON MEDICAL COMPANY, INC.
919 THIRD AVENUE • NEW YORK, N.Y. 10022 • (212) 638-4420

PROGRESS REPORT ON THE PILOT STUDY
"DOUBLE-BLIND SAFETY AND EFFICACY EVALUATION OF PHENYLPROPANOLAMINE HCl IN EXOGENOUS OBESE PATIENTS WITH CONTROLLED HYPERTENSION"

Chief Investigator:

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Submitted to:

Thompson Medical Company, Inc.

July 16, 1982

Prepared by:

K.M. Farragher

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I. STUDY PURPOSE

The purpose of this study is to evaluate the efficacy, tolerance, and safety of phenylpropanolamine HCl (PPA) vs placebo in the treatment of exogenous obesity in patients with controlled, stable hypertensive diseases.

II. PATIENT POPULATION PROFILE

The patient population profile included twelve (12) patients in the age range of 25 to 67 years with exogenous obesity and controlled, stable hypertensive disease.

A controlled, stable hypertensive disease was defined as diastolic blood pressure at or below, 94mmHg. The hypertensive disease state was controlled with thiazide, with and without concomitant potassium supplements.

Exogenous obesity was defined as at least 10%, but not more than 55% overweight as calculated using the revised Metropolitant Life Insurance Company Statistical Book 47:1, 1966.

III. PATIENT EXCLUSION CRITERIA

1. Patients currently using concommitant medication which would interfere with the evaluation of safety and/or efficacy, i.e. MAO inhibitors.
2. Patients who have suffered a recent (3-6 months) myocardial infarction or with severe cardiac decompensation.
3. Patients who have had recent (3-6 months) surgery.
4. Patients with elevated venous blood pressure.
5. Patients with unstable or accelerated anginal episodes.
6. Patients who exhibit complications of hypertenstion or arteriosclerotic cardiovascular disease, such as cerebral ischemia or uremia.
7. Patients who cannot adhere to the protocol visit schedule.
8. Patients who are pregnant or lactating.
9. Patients who have been on weight reduction programs or medication during the three weeks prior to this study's initiation.

IV. STUDY DESIGN

The study was a single-blind crossover study which extended for six weeks according to the following medication and dosage schedule:

WEEK 1 & WEEK 2	Phenylpropanolamine 25 mg. caffeine 100 mg t.i.d. (one hour before meals)

IV. STUDY DESIGN (continued)

WEEK 3 & WEEK 4 Placebo, b.i.d. (10 a.m. & 4 p.m.); washout period

WEEK 5 & WEEK 6 Phenylpropanolamine 75 mg. o.d. (10 a.m.)

Data was collected according to the following schedule:

INITIAL VISIT (Day 0).............Chest X-Ray, Background & Clinical Data

WEEKLY VISITS.......................Body Weight, Vital Signs (oral temperature, blood pressure, pulse), Appetite Suppression (degree, duration), Side Effects

BIWEEKLY VISITS....................Physical Examination, Supine Electrocardiograph Tracing, Blood Pressure and Pulse ½, 1, 2 & 4 hours after initial dose.

V. STATISTICAL METHODS

Analysis of variance (t-tests) was performed on the differences between baseline values and (a) biweekly treatment group values and (b) biweekly treatment group values taken at ½, 1, 2, and 4 hours for blood pressure and pulse measurements.

These variables were also tested for significant differences for each treatment group during each treatment week (i.e., weeks 1 vs 2, week 3 vs 4, week 5 vs 6).

Laboratory values (glucose, triglycerides, cholesterol, GGTP, SGOT, LDH, sodium, potassium, chloride and oral temperatures) were compared for significiant differences between baseline and end of treatment group values. Also, laboratory values for placebo vs medicated treatments were compared.

Hunger feelings (appetite suppression) and weight loss measurements were examined for differences between baseline and end of treatment group values.

A 95% confidence level was used to test the statistical significance of the data.

VI. STUDY RESULTS

A. PATIENT POPULATION PROFILE

Ten of the initial twelve patients completed the study. Patient #4 and #10 completed the first crossover leg but were discontinued because of protocol violations (using an MAO inhibitor and previous time commitments, respectively). Neither patient reported any adverse reactions.

Table #1 presents the patient population profile in terms of age, sex and weight/height characteristics.

TABLE #1: PATIENT POPULATION PROFILE

	PATIENTS ENTERED	PATIENTS COMPLETED
NUMBER	12	10
SEX		
Male	3	2
Female	9	8
AGE (YRS)		
Mean	54.5	54.4
Range	25-67	23-67
BODY FRAME		
Small	0	0
Medium	7	7
Large	5	3
% OVERWEIGHT		
Mean	26.6%	23.8%
Range	12-54	12-54
INITIAL WEIGHT		
Mean	184.7	178.8
Range	149-284	149-284
IDEAL WEIGHT		
Mean	139.9	137.2
Range	125-184	125-184

B. VITAL SIGNS DATA

1. Blood Pressure and Pulse Data

a. Baseline vs Biweekly Treatment Values

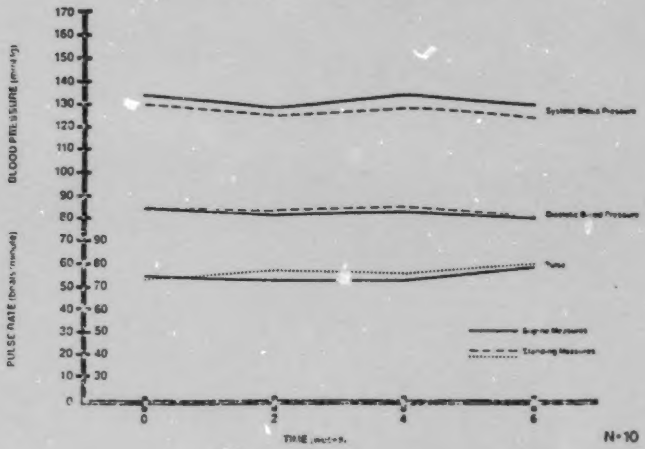
Table 2 lists the mean and range values for blood pressure and pulse values at baseline and at end of each treatment period. Figure 1 displays these values graphically.

No statistically significant differences were found between baseline values and end of treatment values for blood pressure or pulse measurements.

TABLE 2: RANGE VALUES OF BLOOD PRESSURE (mmHg) & PULSE RATE DATA (beats/minute) AT THE END OF EACH TREATMENT PERIOD (Mean Values Within Parenthesis) N=10

MEASUREMENT	BASELINE	WEEK 2 (25mg PPA) 100 mg caffeine	WEEK 4 (Placebo)	WEEK 6 (75 mg. PPA)
Standing Pulse	54-88 (73.0)	64-96 (76.4)	56-88 (75.8)	60-98 (80.0)
Supine Pulse	54-92 (73.3)	56-88 (72.5)	56-84 (73.6)	64-96 (76.2)
Standing Diastolic	74-92 (84.2)	70-94 (82.0)	70-90 (82.2)	64-92 (80.2)
Supine Diastolic	70-94 (83.4)	60-90 (80.0)	62-90 (81.2)	60-90 (79.6)
Standing Systolic	116-142 (130.6)	100-166 (125.2)	114-148 (127.8)	100-158 (124.2)
Supine Systolic	114-170 (133.3)	108-164 (127.8)	112-150 (132.4)	90-150 (129.6)

Figure 1. MEAN BLOOD PRESSURE (mmHg) AND PULSE RATE (beats/minute) VALUES AT BASELINE AND END OF TREATMENT WEEKS.



VI. STUDY RESULTS

1. Blood Pressure and Pulse Rate Data (continued)

b. Baseline vs ½, 1, 2, and 4 Hour Values

Table 3 lists the means and the range of values for blood pressure and pulse measurements at baseline and at ½, 1, 2 and 4 hours following the first medication dosage for all three treatment groups. Figures 2 through 4 display the means of these values graphically.

No clinically significant differences were found between the mean blood pressure and pulse values at baseline, and ½, 1, 2 and 4 hours following the first medication dosage, although eleven statistically significant differences were seen. Clinical insignificance is easily determined by examining (a) the small changes between baseline values and (b) the small differences between "textbook" values for normotensive patients (diastolic blood pressure, 60-90 mmHg; systolic blood pressure, 100-140 mmHg; pulse, 70-90 mgHg) and treatment values.

TABLE 3 RANGE VALUES OF BLOOD PRESSURE (mmHg) & PULSE RATE (beats/minute) DATA AT ½, 1, 2 and 4 HOURS AFTER MEDICATION
N=10
(mean values within parenthesis)

MEASUREMENT	BASELINE	½ HOUR AFTER MEDICATION	1 HOUR AFTER MEDICATION	2 HOURS AFTER MEDICATION	4 HOURS AFTER MEDICATION
		WEEK 1-2 ([illegible] mg PPA, 100 mg Caffeine, t.i.d.)			
STANDING PULSE	56-98 (73.0)	58-88 (75.2)	60-96 (76.8)	56-100 ([illegible])*	56-96 (80.6)
SUPINE PULSE	54-92 ([illegible])	57-84 (69.6)	52-88 (68.[illegible])	72-96 (76.[illegible])	64-96 (76.0)
STANDING DIASTOLIC	76-92 ([illegible])	70-96 (87.0)	80-100 (88.6)*	70-96 (85.9)	72-96 (85.6)
SUPINE DIASTOLIC	70-94 (83.4)	68-96 (85.0)	84-100 (88.0)*	80-98 (87.5)	76-98 (87.8)
STANDING SYSTOLIC	110-142 (130.6)	126-152 (135.6)	110-150 (134.2)	110-160 (137.2)*	110-150 (134.0)
SUPINE SYSTOLIC	116-173 (133.5)	118-172 (136.0)	135-190 (145.4)*	130-170 (145.3)*	1[illegible]-160 (142.[illegible])*
		WEEK 3-4 (PLACEBO)			
STANDING PULSE	64-94 (76.4)	6[illegible]-98 (78.[illegible])	58-100 (78.8)	72-100 (82.0)*	60-96 (79.0)
SUPINE PULSE	58-88 (72.5)	56-92 (72.0)	5[illegible]-94 (71.0)	5[illegible]-88 (7[illegible])	56-88 (73.6)
STANDING DIASTOLIC	70-96 (82.0)	58-96 (81.0)	62-100 (82.8)	56-92 (77.5)	58-90 (77.8)
SUPINE DIASTOLIC	60-90 (80.0)	50-96 (79.6)	76-96 (82.4)	56-90 (78.8)	60-92 (78.6)
STANDING SYSTOLIC	100-160 (125.2)	86-164 (120.[illegible])	90-138 (119.0)	92-160 (118.6)*	75-100 ([illegible])
SUPINE SYSTOLIC	108-164 (127.8)	1[illegible]-172 (125.8)	150-152 ([illegible])	90-158 (12[illegible])	108-160 (128.[illegible])
		WEEK 5-6 (75 mg PPA, O.D.)			
STANDING PULSE	56-88 (73.8)	55-96 (73.4)	68-96 (81.0)	76-120 (85.7)*	75-100 (81.3)
SUPINE PULSE	56-84 (73.8)	56-88 (70.0)	60-90 (75.1)	66-124 (83.6)	65-120 (78.9)
STANDING DIASTOLIC	70-92 (82.2)	70-90 (82.6)	80-94 (85.8)	76-90 (81.8)	70-90 (82.7)
SUPINE DIASTOLIC	62-90 (81.[illegible])	70-90 (83.0)	76-96 (86.[illegible])	76-90 (85.3)	70-98 (85.6)
STANDING SYSTOLIC	114-164 (128.[illegible])	100-160 (129.0)	110-152 (137.8)*	118-162 (1[illegible].6)	110-150 ([illegible].8)
SUPINE SYSTOLIC	112-150 ([illegible].4)	110-146 (135.4)	106-160 (139.6)	138-160 (13[illegible])	106-166 (139.[illegible])

* Statistical Significant Differences (p≤0.05)

Figure 2. MEAN BLOOD PRESSURE (mmHg) AND PULSE RATE (beats/minute) VALUES FOLLOWING TREATMENT ONE (25mg PPA, 100mg caffeine, tid).

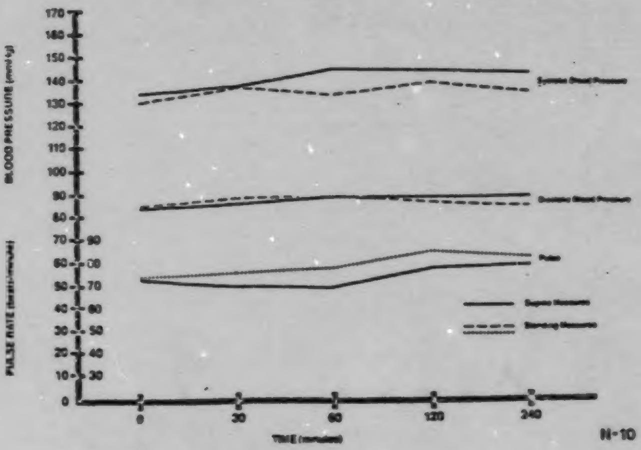


Figure 3. MEAN BLOOD PRESSURE (mmHg) AND PULSE RATE (beats/minute) VALUES FOLLOWING TREATMENT TWO (placebo).

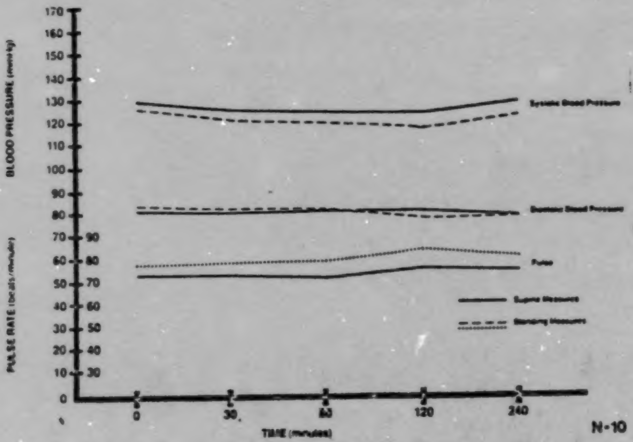
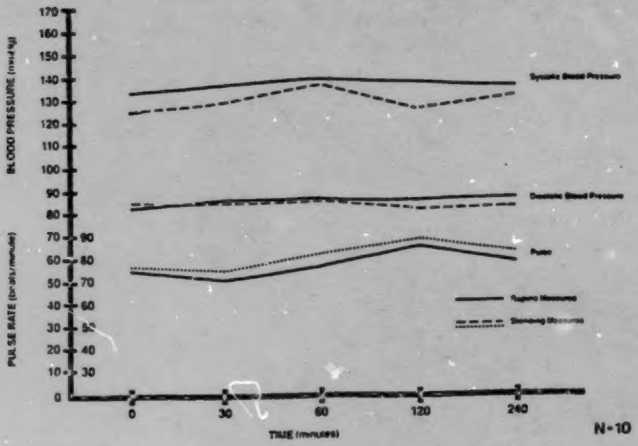


Figure 4. MEAN BLOOD PRESSURE (mmHg) AND PULSE RATE (beats/minute) VALUES FOLLOWING TREATMENT THREE (75mg PPA, OD)



VI. STUDY RESULTS

1. Blood Pressure and Pulse Data (continued)

c. Intraweekly Treatment Comparisons

No significant differences were found between any blood pressure or pulse measurements within treatment weeks in all three treatment groups, as shown in Table 5.

TABLE 5: MEAN BLOOD PRESSURE (mmHg) AND PULSE (beats/minute) BASELINE AND INTRATREATMENT WEEK VALUES (n=10)

	TREATMENT 1 (25 mg PPA, 100 mg caffeine, t.i.d.)		TREATMENT 2 (Placebo)		TREATMENT 3 (75 mg PPA, od)	
BLOOD PRESSURE	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6
Diastolic (Standing)	85.2	82.0	84.2	82.2	81.4	80.2
Diastolic (Supine)	83.6	80.0	80.4	81.2	83.4	79.0
Systolic (Standing)	137.4	125.2	128.0	128.2	127.2	124.2
Systolic (Supine)	130.8	127.8	134.0	132.4	133.8	129.6
PULSE						
Pulse (Standing)	78.6	76.4	76.6	75.8	78.5	80.0
Pulse (Supine)	73.6	72.5	73.0	73.6	73.6	76.2

2. Laboratory Blood Analysis Data

a. Baseline vs Biweekly Treatment Values

No significant differences were found between any laboratory variables for all study treatments. These results are presented in Table 6.

TABLE 6: MEAN LABORATORY VALUES FOR BASELINE AND BIWEEKLY TREATMENT VALUES (N=10)

LABORATORY TEST	NORMAL RANGE	BASELINE	TREATMENT 1 (25mg PPA,100mg Caffeine,tid)	TREATMENT 2 (Placebo)	TREATMENT 3 (75mg PPA,od)
Glucose (mg/dl)	65-110	106.7	108.0	106.2	100.7
Triglycerides (mg/dl)	74-142	208.3	172.9	184.5	176.0
Cholesterol (mg/dl)	150-300	241.5	249.1	234.3	243.9
GGTP (u/l)	7-33	47.6	20.8	17.0	20.0
SGOT (u/l)	10-50	26.6	27.3	26.5	21.6
LDH (u/l)	100-225	176.4	180.9	166.6	149.3
Sodium (meQ/l)	135-145	139.6	140.6	141.3	140.2
Potassium (meQ/l)	3.5-5.0	4.2	4.3	4.2	4.1
Chloride (meQ/l)	95-110	101.9	102.9	102.2	100.2

VI. STUDY RESULTS

2. Laboratory Blood Analysis Data

a. Baseline vs Biweekly Treatment Values (continued):

Table 7 lists the patients with laboratory values outside the normal range. Laboratory values which increase continually or sporadically are listed in the bottom half of the table.

TABLE 7: PATIENTS WITH LABORATORY VALUES OUT OF THE NORMAL RANGE (N=10)

Patient Number	Glucose	Trigly-ceride	Choles-terol	GGTP	SGOT	LDH	Sodium	Potassium	Chloride
1				*(1)					
2	•	*(6)							
3		*(1)							
5	•	•							
6	*(4)								
7	*(2)	•	•						
8	*(1)	*(3)							
9	•	•	•						
11		*(1)	*(1)		•(3)	•(1)			
12		•							

MEASUREMENT	PATIENT NUMBER	BASELINE	WEEK 2 (25mg PPA,tid, 150mg caffeine)	WEEK 4 (Placebo)	WEEK 8 (75mg PPA,od)
Glucose (mg/dl)	2	105	120	87	87
	5	98	100	120	95
	9	113	106	128	123
Triglycerides (mg/dl)	3	[illegible]	170	133	181
	7	[illegible]	[illegible]	[illegible]	[illegible]
	9	[illegible]	[illegible]	[illegible]	[illegible]
	12	[illegible]	[illegible]	[illegible]	[illegible]
Cholesterol (mg/dl)	7	463	[illegible]	[illegible]	[illegible]
	9	[illegible]	271	[illegible]	[illegible]
LDH (u/l)	12	220	300	[illegible]	290
SGOT (u/l)	12	45	33	72	19

(•) Values decreased or increased sporadically from baseline values.

(*) Values decreased or increased continually from baseline values.

( ) Number of values outside the normal range.

— Values above the normal range are underlined once.

═ Values below the normal range are underlined twice.

VI. STUDY RESULTS

2. Laboratory Blood Analysis Data (continued):

b. Biweekly Laboratory Values

With the exception of one instance, statistical comparisons of lab values between treatment one, two and three showed no significant differences. The exception occurred between treatment one (25mg PPA, 100mg caffeine, tid) and treatment three (75mg PPA, od) glucose levels. At week 2, the mean glucose value was 108.0mg/dl and at week 6 the mean glucose value had decreased to 99.4mg/dl ($p<.05$), a change of 8.6mg/dl.

3. Oral Temperature Values

Oral temperature values did not fluctuate. All temperature values were 98.6.

C. WEIGHT LOSS DATA (Efficacy Analysis)

Patients receiving phenylpropanolamine lost more than 1 pound per treatment week as shown in Table 8.

TABLE 8: MEAN CUMULATIVE WEIGHT LOSS/WEEK (lbs)

TREATMENT	WEIGHT LOSS
25mg PPA (tid)	-1.9
75mg PPA (od)	-1.4
Placebo	-0.63

These values exceed the FDA finding of a mean weight loss of 1 pound per week among 10,000 patients receiving prescription weight loss aids.

Ninety-three percent (93%) of the patients reported that they experienced none or slight hunger feelings after receiving 25mg PPA (tid), or 75mg PPA (od). Seventy-one percent (71%) of the patients reported that they experienced moderate or marked hunger feelings after receiving treatment 2 (placebo).

D. SIDE EFFECTS

One patient (#7) reported feeling nausea and dizziness during the first week of medication (25mg PPA, t.i.d.).

VII. CONCLUSIONS

The lack of clinically significant differences between baseline and ½, 1, 2 and 4 hour blood pressure and pulse values provides safety data for the use of phenylpropanolamine appetite suppressant products by stable, controlled hypertensive patient populations. In addition, differences between baseline and end of treatment values showed non-significant differences for all comparisons plus intraweekly treatment comparisons showed no significant differences. These results justify the continuation of this pilot study.

The effectiveness of phenylpropanolamine appetite suppressant aids for stable, hypertensive populations was also substantiated in this pilot study. The patients receiving 25mg (tid)* and 75 mg (od) showed a mean weight loss of 1.9 pounds and 1.4 pounds per week, respectively, which exceeds the FDA finding of a mean weight loss of 1.0 pounds per week for 10,000 patients receiving prescription weight loss aids, as presented in the "Review of Amphetamine-Like Drugs by the FBD" in Obesity in Perspective (Vol II, Part II, Bray, GA, ed. Washington, DC, Government Printing Office, 1976, pp.441-443). The incidence of reduced hunger feeling (86%) was greater among patients receiving active medication.

*plus 100mg caffeine.

[redacted]
1700 Pennsylvania Avenue, N.W./Washington, D.C. 20006/Phone (202) 393-1700

August 27, 1982

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs
Dockets Management Branch (HFA-305)
Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Reply Comments: Weight Control Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Advance Notice of Proposed Rulemaking, 47 Fed. Reg. 8466 et seq. (February 26, 1982), Docket No. 81N-0022

Dear Sir:

Comments were due on July 26, 1982, on the above proposal, which consists of a Report and Proposed Monograph of the Advisory Panel on OTC Miscellaneous Internal Drug Products, convened by the Food and Drug Administration under its OTC Drug Review. Reply comments were to be submitted by August 27, 1982.

These reply comments are filed on behalf of The Proprietary Association, a 101-year-old trade association, the active members of which are engaged in the manufacture and distribution of nonprescription or over-the-counter medicinal products. Members of the Association are subject to the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301, et seq.) and are interested in and affected by this proposal.

These reply comments are not intended to supersede any which may be filed by individual members of the Association.

Comments Which Assert that Phenylpropanolamine Causes High Blood Pressure or Other Adverse Reactions.

The principal concerns of the Center for Science in the Public Interest (CSPI) regarding the safety of

REPRESENTING MANUFACTURERS OF NONPRESCRIPTION MEDICINES phenylpropanolamine rest on what CSPI describes as "the known tendency of PPA to raise blood pressure...." (CSPI, p. 5.) To the contrary, there have been no studies submitted or cited by any participant in this proceeding that support the proposition that PPA has a "known tendency" to raise blood pressure at the dosage levels recommended in the ANPR.

In its discussion of the relationship between PPA and hypertension, CSPI states that after the Panel's report on weight control products containing PPA was submitted to FDA in 1979 "several reports of alarming cardiovascular reactions to recommended quantities of PPA appeared in the the medical literature." (CSPI, p. 6.) "In response to this evidence," CSPI goes on to state, "FDA took regulatory action to remove from the market all weight control products containing single, immediate-release doses of greater than 37.5 mg of PPA and timed-release doses of greater than 75 mg." (CSPI, p. 6.) This is incorrect. In actuality the action by FDA to limit products to single, immediate-release doses of not greater than 37.5 mg of PPA and timed-release doses of not greater than 75 mg was based on the agency's position that products which contained higher doses were not marketed OTC prior to December 5, 1975, and were, therefore, "new drugs." (47 Fed. Reg. 8468, February 26, 1982.)

CSPI cites the double-blind trial reported by Horowitz, et al., in 1980 as substantiation for its assertion that the available evidence does not support a Category I classification for any dose of PPA. The Association commented extensively on the Horowitz study (see p. 5 of PA Comments), and now wishes to add that the study by C. A. Mitchell, referred to on page 7 of our comments, did not report comparable results with the 50 mg timed-release portion of the study. In a cross-over study, six normotensive volunteers received placebo or 50 mg PPA plus 0.25 mg belladonna alkaloids. Blood pressure and pulse were recorded every 15 minutes for the first 90 minutes and every 30 minutes for the next 90 minutes after dosing. Mitchell reported no statistically significant differences between drug and placebo on mean arterial pressure or pulse.

Nor did 11 percent of those persons who received 50 mg of PPA in a timed-release form in the Horowitz study develop "significant, sometimes severe diastolic hypertension," as CSPI asserts. (CSPI, p. 6.) Horowitz reported that four of the 37 subjects had a diastolic reading of 100 or more, and reported that one of those four participants had a maximum supine blood pressure of 145/110 mm Hg. Presumably the subject with the 145/110 mm Hg. reading had the highest diastolic reading of the four subjects with readings of 100 or more. This is not equivalent, however, to reporting that the subjects had "severe diastolic hypertension," as CSPI states, nor did Horowitz so classify those subjects. Moreover, although Horowitz stated that three subjects in the 85 mg portion of the study received anti-hypertension therapy, he did not report that any of the subjects in the 50 mg portion of the study received anti-hypertension therapy.

CSPI further asserts that one would expect the elevated diastolic blood pressure readings reported in the subjects in the Horowitz study who received a 50 mg timed-release capsule to occur in more people if a 75 mg dose were ingested. (CSPI, p. 7.) In fact, the Noble study cited on page 7 of our comments demonstrates that no such result occurred.

The speculations of CSPI are further negated by the fact that in 1981 approximately five billion doses of PPA were taken in the form of cough/cold and weight control OTC products, with only a handful of reports of adverse reactions, which appear to be either idiosyncratic or due to overdoses.

The comments of the California Association of Neurological Surgeons, Inc. and those of Arthur F. Shinn, Pharm. D., Beecham Laboratories, raise a similar safety concern when PPA is ingested. However, the reports cited in those comments simply do not indicate that there is a relationship between PPA and the reactions reported when PPA is ingested at the dose levels recommended in the ANPR. The comments of the California Association of Neurological Surgeons, for example, report three cases of adverse reactions after ingestion of PPA. Case 1 and Case 2 are, respectively, a report of an overdose of an OTC weight-control product, and a report of ingestion of an illegal "look-alike" product. Case 3 is a report of an adverse reaction after the ingestion of an OTC "diet pill," which is not otherwise identified. As to Case 3, it should also be noted that the report states that vomiting occurred immediately after ingestion and that the adverse reaction occurred after the vomiting. It is unlikely, therefore, that the adverse reaction resulted from the ingestion of the "diet pill."

Similarly, the reports cited by Shinn involved overdoses, ideosyncratic reactions and/or illegal combinations. Case 1 involved a patient with a history of epilepsy who had a seizure apparently coincidentally with the ingestion of two combination cough/cold products. In Case 2 the patient had consumed three to five ounces of whiskey just prior to ingesting two "black capsules," each containing a combination of 200 mg caffeine, 25 mg ephedrine and 50 mg PPA, a combination which FDA has since declared to be an unapproved "new drug." (47 Fed. Reg. 35344, August 13, 1982.) Case 3 again involved two "black capsules" containing the same illegal combination.

CSPI asserts that the recommended label warning is inconspicuous and inadequate to protect persons who have hypertension, heart disease, diabetes or thyroid disease from ingesting weight control products containing PPA. (CSPI, pp. 12-13.) As an examination of the label warnings on these products shows, the warning is clear and conspicuous, as, indeed, Section 502(c) of the Act and FDA's regulations require it to be.

CSPI further asserts that "[c]onsumers have an understandable tendency to believe that drugs available on an OTC basis are safe for most potential purchases,...." (CSPI, pp. 12-13.) We believe that this is true and that it is also fully consistent with the philosophy of making medication available to the consumer on an over-the-counter basis. In stating that consumers do not read labels because they believe that OTC medicines are unqualifiedly safe for everyone, CSPI is not really questioning the safety of PPA as an OTC; it is really questioning the fundamental principle of self-medication itself -- that people are capable of using an OTC safely and effectively if they follow labeling directions.

Comments Which Assert that Phenylpropanolamine is Unsafe Because of Alleged CNS Effects

CSPI states that PPA is unsafe for use in weight control products because of reports of adverse CNS effects resulting from the ingestion of PPA. CSPI concedes that "[n]one of these incidents proves definitively that PPA can cause mental derangement," but contends that "the structural similarity is there..." between PPA and the amphetamines, adrenaline, and related sympathomimetic amines. (CSPI, p.3.) CSPI couples the structural similarity with case reports in the United States and other countries linking PPA with adverse CNS effects. CSPI cites several reports, including the Dietz survey listed in the preamble to the ANPR as Reference 9, as support for the proposition that there have been "scattered accounts that even normal doses of PPA may sometimes cause or aggravate psychotic episodes, hallucinations, or other severe behavioral aberrations that mimic amphetamine reactions." (CSPI, p.3.) We submit that the Dietz survey does not support the proposition that there are adverse CNS effects associated with the use of PPA at the dosage levels of the products currently marketed or the dosage levels proposed by the Panel. As CSPI points out, the Dietz survey is composed of scattered accounts. (CSPI, p. 3.) In addition, the seven cases referred to in the Dietz survey, which were taken from record cards of patients in emergency rooms, are accounts of isolated cases of individual adverse reactions. There was no possibility of verification of the actual doses of PPA taken since the PPA was not taken under controlled conditions, and there was no follow-up to determine whether the symptoms reported were repeated under the same or different circumstances.

The other reports cited by CSPI (CSPI, p.3, fn. 9) also fail to support the proposition for which CSPI cites them. With regard to the Achor and Extein report of precipitation of bipolar affective disorder in three patients who had been taking diet-aid products containing PPA, one patient had been taking twice the recommended dose, and the dosage for the other two patients was not reported. Therefore, one of the cases clearly involved an overdose, and the remaining two cases may have as well. Furthermore, according to the report, all three patients had histories of mood disorders. Finally, the report did not describe the patients' psychiatric status immediately prior to taking the diet aids, or after they were withdrawn. It is therefore impossible to evaluate whether PPA played any role in the psychiatric episodes reported.

The Schaffer and Pauli report cited by CSPI involved one patient who ingested three to five pills each day from two separate bottles of diet pills. Obviously, the reaction of that patient is of no use in any evaluation of PPA.

The report by Norvenius, et al., cited by CSPI, dealt with complaints to the Swedish Adverse Drug Reaction Committee. It is unclear from the report whether the total number of complaints was 61 or 66. In any event, five patients were reported to have had psychotic episodes, but the report does not give dose levels for any of the patients. Since 48 of the patients were under age 16, it is probable that many of these patients ingested accidental overdoses. Moreover, the report specifically notes that one 17-year-old male had taken "large" quantities of a PPA and brompheniramine combination product. In view of the absence of data on the precise dosage ingested in each case, the report essentially has no probative value.

The Wharton report relied upon by CSPI describes a psychotic episode in a patient taking a cold medication containing 12.5 mg of PPA, phenyltoxolamine, phenacetin and thonzylamine. He exhibited paranoid psychosis after an eight-day period in which he had ingested 30 tablets. He was treated for the paranoid psychosis, but eight weeks after recovery he suffered a similar reaction, although he was not taking the cold medication at the time. Therefore, the psychotic reaction apparently did not result from the ingestion of PPA.

Finally, CSPI cites the Kane and Greene report of three patients who took nasal decongestants containing PPA. The reaction of two of the three patients simply does not support the Center's position. One of the patients had previously been treated for undifferentiated schizophrenia. That patient's reaction may well have resulted not from the ingestion of PPA but from a preexisting mental condition. Another patient had used "two bottles" of the decongestant within one week. There is no indication as to the actual amount of PPA taken at any one time. Accordingly, once again, the report cannot be cited as support for any proposition concerning PPA.

To summarize, the five published reports discussed above include 13 patients who experienced psychotic episodes. Three of the patients were children 8 years old or younger, who probably ingested accidental overdoses, and one patient was a 17-year-old who reportedly had taken "large quantities" of a PPA and brompheniramine combination product. Among the remaining nine patients, one had taken more than the recomended dose; another may have taken more than the recommended dose (the only information available was that the patient took "two bottles"); one apparently took two PPA-containing preparations, but dosage was not specified; four had histories of affective illness or schizophrenia and one of these took more than the recommended dose; and one patient experienced another psychotic episode eight weeks after he had discontinued use of products containing PPA. Moreover, it should be reiterated that substantially all of the complaints reported by Norvenius, et al., were complaints of restlessness, irritability, etc. Furthermore, these reports primarily involved children 15 years old and younger and, therefore, most of the cases undoubtedly involved accidental ingestions or overdoses.

CSPI also cites another case in which alleged adverse CNS reactions occurred. (CSPI p. 7.) The case involved a 44-year-old woman who developed "confusion [and] grand mal seizures" approximately an hour after taking a 75 mg timed-release weight control capsule. As a careful reading of the report of the incident indicates, the woman had previously experienced grand mal seizure reactions to cough/cold medications. Therefore, her grand mal seizure reaction was idiosyncratic. There is, moreover, no established contraindication for sympathomimetic drugs for epilepsy.

Relying on Porter & Dietsch, Inc. v. Federal Trade Commisson, 90 FTC 770 (1977), aff'd, 1979-2 Trade Cases ¶ 62,796 (7th Cir. 1979), CSPI asserts that PPA is unsafe because the advertising for weight control products containing PPA which does not include a health warning is misleading. (CSPI, p. 13). The relevancy to this proceeding of the FTC's action in that case is dubious at best. In any event, CSPI misstates the scope of the ruling in Porter & Dietsch. The holding was limited to the particular advertisements at issue in that case. It was not applicable to all PPA-containing weight control products. Moreover, as FDA knows, the Panel recommended a number of label warnings for these products, as discussed above.

There is an absence of any evidence establishing that adverse CNS reactions are a side effect of the ingestion of PPA at the dosage levels proposed by the Panel. In fact, the marketing experience of cough/cold and weight control products containing PPA in the United States is support for the proposition that adverse CNS reactions are not a side effect of the ingestion of PPA. Furthermore, the marketing experience is supported by a recent double-blind, cross-over study by Seppala, reported in the British Journal of Clinical Pharmacology. [17] The Seppala study, which also included antihistamines that provided an active control, reported no euphoric effect and an improvement in perception and reaction accuracy following ingestion of PPA at a 50 mg dose level. Seppala stated in conclusion that "[i]t is noteworthy that mood elevation...was not noted after [treatment with] phenylpropanolamine." Accordingly, in view of the results of the Seppala study, the accumulated experience from the testing and marketing of cough/cold and weight control products which fails to indicate that ingestion of PPA in the doses proposed by the Panel results in adverse CNS reactions, and the fact that the cited reports of adverse CNS reactions are either reports of ingestion of doses above the recommended dosage level or are isolated incidents, we submit that no evidence has been identified that indicates that ingestion of PPA at the recommended doses is unsafe because of possible adverse CNS reactions. We believe, therefore, that further clinical testing is unnecessary in order to evaluate the safety of PPA at the dosage levels under consideration.

CSPI, citing a letter from the British Department of Health and Social Security, states that only one PPA weight control product is marketed in Britain and that the product is a prescription drug, and implies that the FDA should adopt a similar policy with respect to weight control products containing PPA. (CSPI, p. 13.) It should be noted that Britain does permit the marketing of OTC drugs containing PPA. Menley and James markets Contac, its OTC cough-cold product containing PPA, in Britain.

Comments Which Assert that PPA Is Unsafe Because it is a Drug of Abuse

CSPI and G. B. Stickler, M.D., cite drug abuse as a reason for placing PPA on prescription. (SCPI, pp. 3-5; Stickler, p.2.) CSPI relies on Natonal Clearinghouse for Poison Control Center reports and Stickler, citing no sources, simply asserts that PPA "is the number one street-drug, at least in Minneapolis and probably in other cities in this country." (Stickler, p. 2.)

The Association has several comments on the points raised by CSPI and Dr. Stickler with respect to PPA and drug abuse.

(1) National Clearinghouse for Poison Control Centers (NCPCC) Data.

(a) Extrapolations of NCPCC data must be made with caution since the data are derived from only 10% of the nation's poison control centers, and the 10% are not necessarily a valid sample.

(b) The data reflect all reports of ingestions or other incidents, whether serious or not. Most of the reports discussed by CSPI with respect to PPA were made by telephone, rarely involved hospital contact and, on the average, resulted in mild, if any, side effects.

(c) As CSPI concedes (CSPI, p.5), "a large percent of the Clearinghouse PPA cases involved children ...." The Association notes that this percentage is large indeed - over 40. That is, over 40% of the cases involve children under 5 years of age. Placing an ingredient on prescription to eliminate unsupervised ingestions by children is not, the Association submits, a legal or wise measure.

As FDA knows, The Proprietary Association and its members have long been active in working to reduce unsupervised ingestions of medicines by children. The Association has participated in government-sponsored conferences and various educational activities on the subject, while its members have been experimenting with, testing, improving, and using various forms of "special packaging" since 1955. Needless to say, the Association supports CSPI's attempt to reduce accidental ingestions, including ingestions by children, of the products subject to this proposal. The Association believes, however, that attempting to combat such ingestions by placing a drug on prescription on the basis that it is "not generally recognized as safe" for OTC use is not proper.

Section 201(p) of the FDC Act defines a "new drug" as one which is "not generally recognized ...as safe and effective under the conditions prescribed, recommended, or suggested in the labeling thereof...." (Emphasis added.) In so defining the term, Congress recognized that any drug can be unsafe if used incorrectly, such as taken internally when it should be used topically and/or taken in excessive amounts. Congress therefore sought to address the question of whether a drug is safe by considering the safety of the drug in connection with the adequacy of its labeling, including its dosage recommendations, method of administration, warnings, and other precautions. Therefore, unless the labeling of the products subject to the proposal prescribes, recommends, or suggests ingestion of amounts which are toxic, such products do not meet the statutory definition of "new drug."

The Consumer Product Safety Commission (CPSC), on the other hand, has the express Congressional mandate "to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting" these and other products by requiring special packaging where appropriate. (140 U.S.C. 1472(a)(1).) Accordingly, the Association suggests that CSPI submit to CSPC what information it has on accidental ingestions of such products by children. FDA, however, is without authority to proceed against such products as "new drugs."

Nor is placing these products on prescription necessarily a useful means of protecting children from the dangers of unsupervised ingestion of drugs. Unsupervised ingestion by children is a function of the accessiblity of the drug to children and the adequacy of parental supervision, not of the legal status of the drug as prescription or OTC.

(d) The Clearinghouse data include a number of suicide gestures. The Association notes that none of the gestures succeeded. Moreover, the safety of OTCs, which are products intended to be taken according to label directions, cannot properly be judged on the basis of data regarding their use in attempted suicides.

(e) For a general but more detailed discussion of the data contained in the August, 1981 NCPCC Bulletin, the Association is enclosing as Attachment A written comments of Charles Winick, Ph.D. Dr. Winick is a Professor at the City University of New York Graduate School, co-editor of the Journal of Substance Use and Abuse, a contributing editor of the Journal of Drug Issues and Addictive Diseases, and a longtime consultant to, and principal investigator on, many projects funded by federal government agencies concerned with drug abuse.

(3) Potential for Abuse of Phenylpropanolamine

CSPI states that the Griffith, *et al*., study which indicated that PPA lacks abuse potential is of questionable significance. No basis for this criticism is given. The Griffith study was well-controlled and conclusively established that drug self-administration procedures with laboratory animals have provided an important conceptual and methodological focus for the pre-clinical assessment of abuse potential. In this study, conducted at Johns Hopkins University, a quantitative ratio measure was developed which permitted comparison between the reinforcing potency of either phenylethylamine anorectics and cocaine in laboratory baboons. The well-controlled study clearly demonstrated that PPA has a zero potential for abuse.[2] Seppala confirmed this in humans, finding no mood-elevating component from 50 mg immediately available doses.[3]

(4) "Amphetamine Look-Alikes"

(a) CSPI questions the safety of PPA for what the Center sees as the ingredient's contribution to drug abuse from the sale of "amphetamine look-alikes," described by CSPI as combinations of PPA, ephedrine, and caffeine. (CSPI, p. 3.) The Association notes that such combinations are not Category I combinations nor is anyone, to the Association's knowledge, proposing that they be placed in Category I. They are thus not relevant to discussions of PPA when used according to the terms set forth in the ANPR. Indeed, FDA has recently taken the position that such combinations are unapproved "new drugs." (47 Fed. Reg. 35344, August 13, 1982.)

(b) Since 1980, 43 states have considered and 33 have enacted legislation which prohibits trafficking in what CSPI describes as "amphetamine look-alikes." Both the U.S. Drug Enforcement Administration and the American Medical Association have developed model bills along this line. The Association understands that in states which have passed such legislation, the problems of abuse of such "look-alikes" has substantially declined. In addition, both FDA and the Post Office Department have instituted seizure actions against a number of manufacturers of such products.

(c) As noted earlier, Dr. Stickler asserts that PPA "is the number one street-drug, at least in Minneapolis, and probably in other cities in this country." (Stickler, p.2.) It appears that what Dr. Stickler is discussing is not PPA in the recommended dose but rather PPA in the illegal combinations discussed above.

Comments Which Question the Effectiveness of Phenylpropanolamine

On page 1 of its comments, CSPI states that one of its concerns regarding weight control products containing PPA is the lack of evidence to support claims of efficacy. CSPI attributes this lack of evidence to the drug manufacturers' alleged refusal "to reveal to the scientific community details of most of the studies purported to back claims of efficacy." Needless to say, all studies submitted to FDA under its OTC Drug Review on PPA are public.

CSPI also states that the Panel's conclusion that the new studies presented to it (Refs. 6 through 11) established the efficacy of such products was "qualified by the statement that 'each of these studies is defective in one or more important ways'." (CSPI, p. 15.) This statement is incorrect. The Panel concluded that PPA is effective and their finding was unanimous. What the Panel in fact stated was that:

> While each of these studies is defective *in one of (sic) more important facets covered by the Panel's proposed protocol*, the Panel believes that the combined evidence of these studies does establish the effectiveness of phenylpropanolamine hydrochloride. (47 *Fed. Reg.* 8475, February 26, 1982.)(Emphasis added.)

CSPI states that the results from the 10 double-blind studies in the public docket do not "support any claim of efficacy." (CSPI, p. 19.) To the contrary, the following data represents the weight loss achieved by patients on phenylpropanolamine and patients on placebo in eight clinical studies presented to the Panel:

Average Weight Loss Per Week

Phenylpropanolamine	1.16 lbs.
Placebo	.56 lbs.
The difference is	.60 lbs.

Moreover, several years ago FDA evaluated 210 double-blind studies in which prescription appetite suppressant products were compared against placebo. These studies represented 105 new drug applications and contained data on nearly 10,000 patients. Scoville[3], in reporting on these results, indicated that of the 4,543 patients on active drug and 3,100 patients on placebo, the weight loss averaged 0.56 pounds per week more for each patient on active drug than on placebo. The results with OTC products containing PPA compare favorably with this result. The average weight loss achieved by patients on the phenylpropanolamine program was .60 pounds *more* than the weight loss achieved by the patients on the placebo-plus-diet program. It is also important to point out that, when phenylpropanolamine was evaluated in these double-blind clinical studies against either a lactose capsule or an active prescription medication, each patient was given, in addition to medication, a 1250 calorie diet, as well as explicit directions from a physician. In other words, in each case the "placebo" was associated with a diet designed to cause loss of weight under the direction of a physician. Therefore, the amount of weight loss achieved by patients on the phenylpropanolamine program was even more significant because the PPA was being compared with another active program, that is, reduced diet and medical directions as well as placebo.

In conclusion, we submit that the cited studies are sufficient to support the efficacy claim made by the various manufacturers, as the Panel concluded.

CSPI cites the FTC decision in the Porter & Dietsch case, discussed above, as if it were a finding on the ineffectiveness of PPA for weight loss. (CSPI, p. 14.) Again, this misstates the case. The question put at issue by the complaint in Porter & Dietsch was "not whether the claims of weight loss are false but instead whether at the time they were made [Porter & Dietsch] possessed reasonable substantiation for them." Porter & Dietsch, Inc., 1976-1979 CCH FTC Complaints and Orders ¶ 21,320 at 21,329. The Commission made no finding as to the efficacy of PPA as an anorectic. Porter & Dietsch, supra at 21,331.

CSPI also asserts that weight control products containing PPA are of no long term benefit because users may regain weight when use is discontinued. OTC weight control products containing PPA are appetite-suppressants which are marketed as an adjunct to assist the motivated consumer on a diet. The products are marketed with diets that are based on a reduction in caloric intake, and the labelling states that weight control will occur only if the product is taken while caloric intake is reduced. Nor do these products claim that weight will not be regained if the person's caloric intake is increased.

Moreover, there is evidence which contradicts CSPI's assertion. Dr. Stanley Shachter, Professor of Psychology at Columbia University, recently concluded a long-term study to determine whether overweight patients continue to maintain reduced weight after a successful weight-loss program.[1] Asked about their weight histories, of 40 people who were obese at the outset, 25 reported losing at least 10 percent of their weight (an average of 34.7 pounds) and therefore becoming no longer obese (that is, within 10 percent of the average weight for their height and age), and remaining at that weight for an average of 11.2 years.

CSPI also cites the statement in the American Medical Association's AMA Drug Evaluations that OTC products containing PPA are "only minimally effective." (CSPI, pp. 14-15.) This characterization has been repeated verbatim year after year, but investigation of the AMA's sources reveals that no scientific studies or proof of any sort are cited by the AMA to support this description of PPA.

Comments Which Question the Validity of the Silverman Study Cited by the Agency and by The Proprietary Association

In its critique of the Silverman study,[5] cited in the Agency's preamble and in CSPI, CSPI states that "the experimental design is flawed in so many important ways that one could have predicted in advance that no effects would be seen." (CSPI, p.9.) When analyzed, this criticism amounts to three points: that the study groups were too small and included only normal, healthy volunteers; that blood pressure values were presented as means for each subgroup, rather than individually; and that only one of the three subgroups was double-blinded. Having consulted with Dr. Silverman, the principal investigator for the cited study, the Association believes that these criticisms of the study are entirely without merit. The so-called "flaws" were all the result of a study design explicitly established in accordance with accepted clinical procedures to eliminate investigator or other bias.

Thus, the pool of 37 volunteers who received active medication was divided into three smaller subgroups at separate sites with a separate group of qualified investigators, each conducting its study independently of the other two subgroups. The total number of volunteers who received active medication was actually the same as the number of volunteers who received active medication (in an overdoes of 85 mg) in one of the Horowitz studies on which CSPI relies so heavily. In fact, CSPI characterizes that Horowitz study as "large." (CSPI, p. 6.) Similarly, the fact that the volunteers were normal, healthy adults was in accordance with accepted practice and was also true of both of the Horowitz studies.

The use of group means to report blood pressures is an acceptable biostatistical procedure.[6]

Finally, the fact that only one of the three subgroups was double-blinded is also not a "flaw" in the study. Each of the three subgroups was treated differently on this score for sound reasons. Study of one subgroup was open in order to simulate the conditions in the actual over-the-counter consumer use of the product. The study of a second group was single-blinded and the study of the third subgroup was double-blinded. The fact that all three subgroups studied under these various conditions produced no significant blood pressure effects reinforces the conclusion that at the tested dosage level, 25 mg, which is the most commonly-marketed immediate release dosage level, phenylpropanolamine produces no adverse blood pressure effects.

In conclusion, it should be noted that the Silverman study is only one of some 60 controlled clinical studies, cited by the Association in its comments, which demonstrate that phenylpropanolamine does not induce hypertension. This mass of positive data, together with almost 50 years of safe use of PPA in this country, clearly outweighs the handful of adverse reports referred to in the CSPI and other comments.

The Association appreciates the opportunity to submit these reply comments.

Sincerely,

THE PROPRIETARY ASSOCIATION

James D. Cope

James D. Cope
President

FOOTNOTES

1/ Seppala, et al., British Journal of Clinical Pharmacology, 12: 179-188, 1981.

2/ Griffith, et al., Biological Psychiatry, 13:1383, 1978.

3/ Scoville, B.A., "Review of amphetamine-like drugs by the Food and Drug Administration," Obesity in Perspective, Fogarty International Center Series on Preventive Medicine, Vol. II (Bray, G.A., ed.), U.S. Government Printing Office, Washington, D. C., 1976, pp. 441-443.

4/ "Don't Sell Habit Breakers Short," Psychology Today, August, 1982.

5/ Current Therapeutic Research, 28: 185-194, 1980.

6/ Goldstine, A., Biostatistics, MacMillan, N.Y., 1968, p. 272.

A

SOME COMMENTS ON POISON CONTROL CENTER REPORT ON PHENYLPROPANOLAMINE

August 1981

Charles Winick, Ph.D.

1. The August, 1981 Bulletin of the National Clearinghouse for Poison Control Centers carried an article on phenylpropanolamine Weight Control Products.

   For the calendar year 1979, there were a total of 144,262 reports of all substances. Of these, 739 were diet aids, of which 328 were named phenylpropanolamine products, or about ¼ of 1% of the total. I obtained this breakdown from several conversations which I had with the senior author of the Poison Control Center report.

2. As someone who has worked for years in the epidemiology of substance abuse, on behalf of the National Institute of Drug Abuse and other agencies, I believe that the tone of the Poison Control Center report on phenylpropanolamine is unduly and inappropriately pessimistic. I do not believe that a valid extrapolation can be made from the actual data to the report's estimate of 10,000 phenylpropanolamine problem cases nationally.

3. The cases reported to the Poison Control Center may or may not be representative of what is actually happening nationally. For example, the country's largest Poison Control Center, in New York City, is one of the 90% of the country's Centers not reporting its experience to the national office. The 10% of the Centers reporting may not represent a valid sample of the national situation.

4. Of the 328 cases with product names, 64% involved no symptoms of any kind and the majority of the remainder did not have significant symptoms. Overall, most cases were telephone-informational communications. Only 6% involved a hospital contact. On the Poison Control Center scale from mild(1) to moderate(2) to severe(3), the phenylpropanolamine reports were, overall, mild(1.4).

5. Over two fifths of the phenylpropanolamine reports were under 5 years of age and almost one third were between 14 and 18 years of age. The former are presumed to be accidental and the latter may have been seeking a "high". If so, they would be disappointed because phenylpropanolamine is not an effective stimulant. The number of accidental cases is another reflection of the importance of the parent's role in management of medications in the home by always keeping medications unavailable to children.

   There were about 200 suicide gestures or attempts. Not only did none of these succeed but there was no fatality in the entire year from phenylpropanolamine, for any reason.

6. The report does not consider the temporary breakout or peaking noted by many epidemiologists when a substance first is employed by larger numbers of people. Because of unfamiliarity with the substance and a barrage of media publicity, when a substance first becomes widely used, there is often a sharp increase in emergency room visits, and calls, reports to poison control centers, mostly for reassurance. After a year or two, the number of such visits and reports declines. It may well be, therefore, that the 1979 reports of phenylpropanolamine incidents represent a temporary cresting which will diminish in the near future.

7. A substantial contributor to reports of problems with phenylpropanolamine is the proliferation of "look-alike" products which may include phenylpropanolamine along with other drugs. I understand that in every state which has enforced restrictions against "look-alike" drugs, there has been a uniform decline in reports of problems with phenylpropanolamine. If the state of Washington bans "look-alikes", this ban, in combination with the cresting phenomenon noted in the preceding paragraph, should lead to a sharp decline in reports of phenylpropanolamine mentions to Poison Control Centers.

Charles Winick

Charles Winick, Ph.D.

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STATEMENT
OF
THOMPSON MEDICAL COMPANY
TO THE
SUBCOMMITTEE ON HEALTH AND LONG-TERM CARE
SELECT COMMITTEE ON AGING
U.S. HOUSE OF REPRESENTATIVES

Mr. Chairman and Members of the Subcommittee:

The Subcommittee kindly offered to Thompson Medical Company the opportunity to testify at the hearing held on July 21, 1983, on the Safety and Effectiveness of Over-the-Counter Drugs and the Elderly.

Thompson Medical is a leading distributor of over-the-counter weight control products containing phenylpropanolamine hydrochloride (PPA). These products are widely and successfully used to suppress appetite, thereby lower food intake, and help reduce excessive weight, which is well understood to be a major cause of disease and premature death.

Thompson Medical also sponsors and supports scientific research in the field of weight control. For this reason, it offered its time before the Subcommittee to a panel of eight medical expert witnesses, all of whom have undertaken studies of PPA, which is an ingredient of the most popular weight control products as well as many cough/cold preparations.

As the experts have testified, PPA has been safely used in the United States for 50 years. It has received more clinical study and evaluation than many prescription drugs, and far more than most other widely used over-the-counter medications. All this evidence clearly demonstrates that PPA is a safe and effective medicine for weight control, when used as directed.

In addition to the expert testimony presented at the hearing, Thompson respectfully submits the following comments of its own to the Subcommittee.

I. ~~II.~~ PPA is Not a Problem for the Elderly

The supplemental statement submitted to the Subcommittee by Charles Winick, Professor of Sociology at the City University of New York, documents his studies showing that fewer than one percent of those who use PPA weight control products are over 60 years old. His statement also documents his conclusion that the weight control industry does not advertise or promote these products among senior citizens. Moreover, as Professor Winick notes, Thompson Medical Company labels its weight control products to advise those under age 18 or over 60 not to use them except under the advice and supervision of a physician.

The Proprietary Association, the OTC drug trade association of which Thompson Medical is a member, has documented the fact that consumers, including the elderly, do read such label warnings and heed them. Thompson Medical fully supports the Association's educational activities to alert the public to the importance of labels and the taking of proper dosages. The fact that these products are so little used by the elderly is also evidence that the elderly do read and follow such label warnings.

Finally, Thompson Medical carefully labels its PPA products to warn against use by those who have high blood pressure, diabetes, heart, thyroid, kidney or other disease or are being treated for high blood pressure or depression. Our product labels also warn against using PPA while pregnant or nursing, except under the supervision of a physician. Thompson Medical also supports consumer education to encourage having one's blood pressure tested on a regular basis.

III. PPA Presents No Safety Problem

A massive amount of clinical data has been submitted to the Food and Drug Administration demonstrating that PPA is safe for use in weight control and cough/cold products.

The attached comments and reply comments submitted to the FDA by The Proprietary Association during 1982 document in detail the more than 60 controlled clinical studies which support the safety and/or effectiveness of PPA. These studies demonstrate that PPA is not a stimulant, has no clinically significant side effects, and specifically does not affect blood pressure, pulse, or mood.

More recent studies at The Johns Hopkins University School of Medicine, which Thompson Medical has submitted to FDA and about which Mr. Frank Funderburk testified before the Subcommittee, confirm that PPA is safe in currently-marketed dosages.

It should be noted that, while many of these studies included normal, healthy adults, a number of them specifically included patients who had pre-existing health problems. For example, the studies referred to on page 13 of the Association's comments dated July 26, 1982, were conducted with patients who had pre-existing hypertension. In one study (Unger, et al.), the patients were suffering from asthma as well as pre-existing hypertension. In another (Bradley, who also testified), all the patients were obese as well as hypertensive. In a third (Noble, also a witness), the overwhelming majority of patients were overweight, and in a fourth (Sebok, another witness), all the patients were overweight.

Nor have the studies excluded the elderly: the Bradley study, for example, included patients ranging in age from 25 to

67, with a mean age of over 54 years; the Hoebel study, submitted to the Subcommittee by Professor Coons, included eight patients between the ages of 51 and 65, out of a total of 70 patients; and the recent Johns Hopkins studies included patients between 18 and 55 years of age. All of these studies concluded that currently-marketed dosage levels of PPA did not significantly increase blood pressure or produce any other side effects.

Careful analysis of Poison Control Center and hospital emergency room data, as Professor Winick's testimony demonstrates, also confirms that PPA is not a dangerous drug. Considering the billions of doses of PPA taken each year in cough/cold and weight control products, the numbers of reported cases (less than one-fifth of one percent of the "mentions") are miniscule.

A study of 70 reported cases by the Intermountain Regional Poison Control Center in Utah, which was submitted to the Subcommittee by Professor Winick, concluded:

> "The lack of serious side effects in either the cases with only PPA or combinations of PPA with caffeine raises questions about the serious reactions noted in earlier published reports."

The massive clinical data so far submitted to the FDA, together with 50 years of safe use of PPA in this country, clearly outweigh the handful of anecdotal reports of individual adverse reactions, most of which, when analyzed, are attributable to frank overdoses or combinations with other drugs. This evidence can only lead to the conclusion that PPA is safe in over-the-counter weight control products, when used as directed.

III. PPA Is Effective For Weight Control

The FDA Advisory Review Panel which studied over-the-counter weight control products unanimously concluded that PPA was safe and effective for weight control, when used as directed. Their finding as to effectiveness was based on eight double-blind studies, which are described in The Proprietary Association's attached reply comments dated August 27, 1982, at pages 11 through 13 and are on the public record of FDA's OTC Drug Review. These studies demonstrated an average weight loss per week of 1.16 pounds with PPA, as compared with .56 pounds per week with placebo.

It should be noted that the "placebo" regimen in these studies (like the PPA regimen) also included giving the patient a 1250 calorie diet and explicit directions from a physician. Thus, in each case the "placebo" was accompanied by a diet designed to cause loss of weight under the direction of a physician. As a result, the much greater weight loss with PPA is even more significant, because it is being compared with another active program of weight loss, consisting of a reducing diet and medical instruction as well as the placebo.

In addition to this substantial clinical evidence, a survey study of nearly 4,000 consumers who used PPA, conducted by Professor Winick, reported even higher weekly weight loss figures, averaging 2 pounds per week per consumer, or 25 pounds over a three month period.

IV. PPA Is Not A Drug Of Abuse

There is abundant evidence that PPA is not a drug of abuse. The evidence for this is cited and discussed in The Proprietary Association's enclosed reply comments dated August 27, 1982, at pages 8 through 11. These studies document that PPA is not a stimulant and does not have the abuse potential of the amphetamines and other powerful stimulants. The recent Johns Hopkins studies further confirmed that PPA does not cause euphoria, amphetamine-like reactions, or sedation.

The Federal government's most recent report from its Drug Abuse Warning Network ranks PPA 102nd among drug "mentions," considerably below such common drugs as aspirin, which ranked 50th.

The "amphetamine look-alikes" or "street drugs," which sometimes contain PPA in combination with ephedrine and large amounts of caffeine, are now illegal in most states and under Federal law. Both FDA and the Postal Service have instituted seizure actions against manufacturers of these illegal combinations. Thompson Medical, along with the rest of the legitimate OTC industry, strongly supports vigorous law enforcement against the trafficking in these illegal and misleading counterfeits.

V. The OTC Review

The FDA is currently conducting an extensive and thorough review of all over-the-counter drugs, pursuant to Federal law and regulations. Among these are weight control and cough/cold products containing PPA. Thompson Medical, with the support of The Proprietary Association, has cooperated fully in the FDA's review of weight control products.

In its review, FDA appointed an expert Advisory Review Panel, which heard extensive testimony over a period of many months and evaluated voluminous written submissions. Thompson Medical appeared before the Panel and made a number of oral and written submissions to it. The Panel then unanimously found PPA to be safe and effective in weight control products, when used as directed. In addition, two other Advisory Panels have also recommended to FDA that PPA be considered safe for other OTC uses.

FDA published the Weight Control Panel Report in the Federal Register for public comment on February 26, 1982, and The Proprietary Association, with the assistance of Thompson Medical, submitted the attached comments and reply comments. Since that time, Thompson has continued sponsoring research on PPA and, as new data has become available, has submitted it to FDA for the OTC Review.

Thompson Medical respectfully urges that FDA, the agency charged by law and equipped to make the necessary scientific judgments about the safety and efficacy of drugs, is the appropriate forum for weighing the medical evidence regarding PPA and all OTC medications.

Thompson Medical Company appreciates having this opportunity to present to the Subcommittee the scientific evidence on the safety and effectiveness of PPA as it is currently marketed in legitimate over-the-counter weight control products.

THE PROPRIETARY ASSOCIATION
1700 Pennsylvania Avenue N.W./Washington D.C. 20006/Phone (202) 393-1700

July 26, 1982

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs
Dockets Management Branch (HFA-305)
Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Weight Control Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Advance Notice of Proposed Rulemaking, 47 *Fed. Reg.* 8456 *et seq.* (February 26, 1982), Docket No. 81N-0022

Dear Sir:

The February 26, 1982 *Federal Register* contained the above proposal, which consists of a Report and Proposed Monograph of the Advisory Panel on OTC Miscellaneous Internal Drug Products, convened by the Food and Drug Administration under its OTC Drug Review. Interested persons were invited to submit written comments by July 26, 1982.

These comments are filed on behalf of The Proprietary Association, a 101-year-old trade association, the active members of which are engaged in the manufacture and distribution of nonprescription or over-the-counter medicinal products. Members of the Association are subject to the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301, *et seq.*) and are interested in and affected by this proposal.

These comments are not intended to supersede any comments that may be filed by individual members of the Association.

General Comments

1. Legal Status of Monographs

The Association notes its continuing position that Monographs issued under the OTC Drug Review are interpretive, as opposed to substantive, regulations. As to this point, the Association herein incorporates by reference: (a) its comments, dated March 4, 1972, on the Proposed Procedures for Classification of Over-The-Counter Drugs; and (b) its comments, dated June 4, 1972, on the Proposed Antacid Monograph.

2. Exclusivity Policy

The Association also notes its continuing position that FDA lacks the statutory authority to prescribe exclusive lists of terms from which indications for use for OTCs must be drawn and to prohibit labeling terminology which is truthful, accurate, not misleading, and intelligible to the consumer.

The Fair Packaging and Labeling Act (15 U.S.C. 1453(a)) requires that an item bear a statement of identity. Section 502(e) of the Food, Drug and Cosmetic Act requires that the label of a drug bear the established name of the drug and, if there be none, the common or usual name. As applied to nonprescription drugs, these requirements are codified in 21 C.F.R. 201.61, which cites both acts as its authority for requiring a "statement of identity" on the principal display panel. Section 508 of the Act authorizes the Secretary to establish official names for drug substances.

None of these statutory provisions reveal any Congressional intent to grant FDA the authority to legislate the exact wording of OTC labeling, such as indications for use, and prohibit truthful labeling terms. Indeed, if manufacturers use some of the terms being prescribed by some OTC Review Panels, their labeling may well be in violation of Sec. 502(c) of the Food, Drug, and Cosmetic Act, which requires that label information be in such terms as to render it likely to be read and understood by consumers under ordinary conditions of purchase and use.

3. Inactive Ingredient Listing

The Association disagrees with the Panel's recommendation (page 8473, third column) that inactive ingredients be listed on the label. First, the listing of inactive ingredients would be meaningless to all but a handful of consumers. Second, it may overstress the importance of such ingredients and obscure far more meaningful information, such as directions for use, warnings, and even the active ingredients. Third, it may confuse consumers. Products which are similar in their purpose and even in the number and identity of active ingredients may differ widely in the number and identity of inactive ingredients. It is perhaps for these reasons that current law does not require that inactive ingredients be listed, as FDA noted in paragraph 75 of the Final Order accompanying the Antacid Monograph [39 F.R. 19862, 19871 (June 4, 1974)].

Specific Comments

1. The Proprietary Association supports the Advisory Panel's classification of phenylpropanolamine hydrochloride as generally recognized as safe and effective for appetite suppression and weight control. The Association's recommendation is based not only on the clinical evidence submitted to the Panel but also on the even more extensive clinical data which has become available since the Panel completed its Report.

The Association supports the Panel's recommendations as to both the safety and the effectiveness of phenylpropanolamine hydrochloride (PPA) for weight control.

The FDA, in its preamble to the Panel's monograph, raised specific safety questions with regard to weight control products and requested further information. At the same time the agency stated that it did not find it necessary to take action to remove from the market products at dosage levels which have a marketing history of use in OTC weight control drug products. The maximum daily dosage levels in these marketed products are an immediate-release dose of up to 37.5 mg and a timed-release daily dose of up to 75 mg phenylpropanolamine, with the total daily dose not to exceed 75 mg in either case [page 8466, second column].

The following comments seek to answer the agency's safety questions by providing the requested information, much of which relates to products not before this Panel or was not available in time for consideration by the Panel, which concluded its work on March 2, 1979.

In its preamble, the agency has raised the following questions:

a. To what extent may phenylpropanolamine hydrochloride induce hypertension in normotensive patients at the recommended dose levels?

b. To what extent may phenylpropanolamine hydrochloride aggravate pre-existing hypertension at the recommended dose levels?

c. To what extent may phenylpropanolamine hydrochloride interact with aspirin and other medications that inhibit prostaglandin synthesis at the recommended dose levels?

These questions are addressed below.

a. To what extent may phenylpropanolamine hydrochloride induce hypertension in normotensive patients at the recommended dose levels?

(1) The Panel had substantial clinical evidence that PPA does not induce hypertension in normotensive patients.

The data submitted to the Panel on safety was more than sufficient, by any standard. At least eight well-controlled clinical studies were submitted to the Panel, each of which substantiated the safety of PPA as an anorexiant. These numerous supportive studies far exceed the usual requirement of two well-controlled clinical studies. These studies are further buttressed by safe consumer use for almost half a century.

Exhibit 1 contains brief abstracts of eight of the safety and efficacy studies made available to the Panel.

(2) The safety reports referred to in the preamble, which were made available after the Panel's report was submitted, should not alter this conclusion.

Nine reports were cited in the preamble as having been made available after the Panel's report was submitted. Two of these re-confirmed the results of the studies considered by the Panel that PPA does not induce hypertension in normotensive patients. These two positive reports are the study by Silverman, *et al*. [Ref. 7] and the studies of 50 mg immediate and sustained release dosages by Cuthbert, Greenberg, and Morley [Ref. 6].

Of the remaining seven reports cited in the preamble, six included isolated cases of individual adverse reactions. These were the case reports of Horowitz, et al. [the portion of Ref. 2 relating to the one 17-year-old woman]; Frewin, Leonello, and Frewin [Ref.3]; King [Ref. 4]; Peterson and Vasquez [Ref. 5]; Lee, Beilin, and Vandongen [Ref.8]; and Deitz [Ref. 9]. In none of these cases was there any possibility of verification of the actual dose of phenylpropanolamine taken since the dose was reported by the patient and not taken under controlled conditions. In at least two of the cases overdoses were stated to have been taken [Ref. 2. relating to the 17-year-old-woman; Ref. 4]. In five of the seven cases, "Trimolets," an 85 mg anorexiant marketed only in Australia, was used. In only two of the seven cases was there any follow-up to determine whether the symptoms reported were repeated under the same or different circumstances. Six of the cases were simply anecdotal in nature. Clearly, any drug, OTC or prescription, has the capacity to cause ideosyncratic reactions in a small number of individual patients.

Only two of the seven adverse reports cited in the preamble were purportedly of controlled clinical studies, both conducted by Horowitz, et al. [Refs. 1 and 2]. To the first of these the agency attributes "the most striking new finding" regarding elevation of blood pressure [page 8466, second column]. However, both of these studies are inappropriate to the agency's safety evaluation of the recommended dose in the United States because the adverse reactions reported by Dr. Horowotz were the result of testing the 85 mg Australian product "Trimolets." This product was labeled as timed-release, but it is open to question whether it did in fact contain a timed-release mechanism. H. I. Silverman, whose study was cited in the preamble [Ref. 7], received and analyzed a small number of "Trimolets." As he has since reported to FDA, Silverman found that the PPA in the product was immediately soluble in water and was not in a sustained release form. (See Exhibit 2, p. 2.)

Silverman's analysis indicates that "Trimolets," which had been used in most of the instances of reported adverse blood pressure effects, delivered in a bolus dose approximately two-and-a-half times the maximum permitted immediate release dose (37.5 mg). The reported adverse reactions therefore were due to overdose.

(3) Finally, there is now overwhelming additional evidence from controlled clinical studies that PPA does not cause hypertension in normotensive patients.

Additional studies, six published and 41 unpublished, which were not submitted to the Panel or referred to in the preamble, support this conclusion. More than 3200 patients were included in these studies, which were not submitted to the Panel because they became available after the Panel completed its work or were conducted on PPA used as a nasal decongestant. However, the dosage levels of PPA in the nasal decongestant studies were comparable to the dosage levels of PPA in weight control products. The published studies include the following:

W. E. Barrett, et al., reporting in Current Therapeutic Research 30: 640-654, November 1981, on a bioavailability study including 18 volunteers, found no adverse effects on vital signs, blood pressure, or ECG, after giving 75 mg sustained action and 25 mg immediate release dosage forms of PPA.

Silverman, et al., reporting in Current Therapeutic Research 28: 185-94, August 1980, found no significant changes in either blood pressure or pulse values after oral administration of 25 mg phenylpropanolamine (od), with and without caffeine, in 37 volunteers.

R.E. Noble, writing in Lancet, June 19, 1982, described three large studies conducted in the past two years on more than 400 obese patients. (See Exhibit 3.) Dr. Noble wrote:

> "Data were gathered on a twelve-week, double-blind, placebo controlled study of 50 mg PPA three times daily...; a double-blind placebo controlled study of 50 mg PPA combined with 200 mg caffeine in controlled-release form; and a single-blind trial of 75 mg PPA in controlled-release form.
>
> "All three dosages caused no significant increase in blood pressure in more than 400 patients. 2 patients experienced noteworthy rises in blood pressure after treatment with 75 mg PPA, but these increases were felt not to be drug related.

> "The mean pooled systolic and diastolic blood pressure in the 50mgx3 PPA/placebo study are shown in the figure.
>
> "Our results confirm that PPA does not cause a significant increase in blood pressure even when the amount ingested (150 mg/day) is substantially higher than the 75 mg dose. There was, on the contrary, a reduction in blood pressure as the studies progressed."

J.H. Black, writing on "The control of allergic manifestations: By phenylpropanolamine (propadrine) hydrochloride" in Lancet 54: 101-102, 1937, reported no blood pressure changes or insomnia in 41 normotensive patients given 48 mg doses of phenylpropanolamine as frequently as every three hours. None of five patients who received 384 mg within two days showed greater blood pressure changes than 10 mmHg systolic. In one hypertensive patient, a 24 mg dose was associated with a decrease in systolic blood pressure, from 170 to 160 mmHg, with no change in diastolic pressure.

W.E. Boyer, reporting on "The clinical use of phenylpropanolamine hydrochloride (propadrine) in the treatment of allergic conditions" in J. Allergy 9: 509-513, 1938, stated that he administered 48 mg doses of phenylpropanolamine every two hours for five days or more with no effects on blood pressure.

C.A. Mitchell, writing on "Possible cardiovascular effect of phenylpropanolamine and belladonna alkaloids" in Ther. Res. 10: 47-53, 1968, reported no pressor effects after giving 50 mg doses of phenylpropanolamine twice daily in 32 normotensive subjects.

The as-yet-unpublished studies which demonstrate that PPA does not induce hypertension in normotensive patients are as follows:

In an eight week, double-blind, randomized study conducted by Rudolph Noble, M.D., Ph.D., in San Francisco, CA, 60 patients were divided into two groups. Thirty patients were given 75 mg of phenylpropanolamine and 200 mg caffeine, timed-release (od), and thirty patients were given 75 mg diethylpropion, timed-release. There was no significant difference in weight loss between the groups.

No significant changes in either blood pressure or pulse measurements were indicated during the test periods in comparison with the baseline measurements.

Marianne Sebok, M.D., Staff Physician at JFK Memorial Hospital, Philadelphia, PA, conducted a six-week, double-blind clinical study of 78 patients who were given either a sustained release capsule containing 50 mg phenylpropanolamine and multivitamins or placebo. The study demonstrated statistically significant weight loss for the active medication group at all measurement intervals. No clinically significant deviations were noted in blood pressure (systolic, diastolic) and pulse and there were no significant side effects.

Stanley L. Altschuler, M.D., Medical College of Pennsylvania, conducted a double-blind, 6-week clinical study of 64 patients who were given either four phenylpropanolamine drops (25 mg) or placebo drops (tid). This study demonstrated statistically significant weight loss at Week 6 for the phenylpropanolamine compared to placebo at the .04 level of confidence. No clinically significant deviations in blood pressure (systolic, diastolic) and pulse were noted, nor were any significant side effects reported.

Hoebel, Krosnick, et al., Department of Psychology, Princeton University, conducted a double-blind, crossover study in which 6 patients took a sustained release 75 mg phenylpropanolamine dose twice daily or placebo capsules. Experimental and placebo groups were reversed after two weeks so that the patients served as their own control. Body weight, pulse, blood pressure and fasting blood glucose levels were recorded three times weekly. There was no significant change in either blood pressure or pulse rate during the 4-week study in which the pre-diabetic patients received twice the daily recommended dose of phenylpropanolamine. The patients' signs were monitored in 12 separate office visits during the period of the clinical evaluation.

In a bioequivalence study at the Massachusetts College of Pharmacy and Allied Health Sciences, 75 mg phenylpropanolamine (od, SR) was compared to 25 mg (tid, IR) in 18 volunteers. No significant blood pressure effects were reported.

In a study of 125 male and female patients by Alvin P. Wenger, M.D., tablets containing 50 mg PPA (SR), 25 mg pyrilamine maleate, and 25 mg pheniramine maleate were compared with placebo for effectiveness as a nasal decongestant. Eighty patients, including all the placebo patients, were double blinded. Blood pressure evaluations were taken at two and four hours after dosage. Overall, there was no major change in blood pressure at the 95% level of confidence. The major side effect reported was drowsiness, with 56% of the PPA patients reporting at least some drowsiness and 38% of the placebo patients. (OTC Volume 040-151)

The following information was provided to the Association by a member company. It is our understanding that the company is submitting this information to FDA in greater detail.

Between 1971 and 1975, blood pressure determinations were recorded in seven studies of healthy adult volunteers to evaluate the bio-availability of PPA from various formulations. Generally, the studies were conducted as crossover trials comparing sustained-release (SR) and immediate-release (IR) formulations administered as single doses. A total of 76 volunteers were included in the studies, and they were administered 211 test doses of PPA. Blood pressure and pulse rate were determined before and on several occasions after administration of each test dose. The following test doses were administered:

> 150 mg IR doses were administered to 35 volunteers on a single occasion during three studies (#2,3,4) (12 received 150 mg as a single dose and 23 received 150 mg in divided doses over 8 hours);
>
> 150 mg SR doses were administered to 48 volunteers on 60 occasions during four studies (#2,3,4,5);
>
> 100 mg IR doses were administered to four volunteers on a single occasion during one study (#4);
>
> 75 mg IR doses were administered to 48 volunteers on 60 occasions during four studies (#1,3,4,5);
>
> 75 mg SR doses were administered to 12 volunteers on a single occasion during one study (#1);
>
> 50 mg IR doses were administered to 12 volunteers on a single occasion during one study (#3);
>
> 36 mg IR doses were administered to 12 volunteers on 24 occasions during one study (#7).

Clinically significant increases in blood pressure were detected only following administration of 150 mg immediate release PPA, and only in five out of the 35 test doses. Even in the five cases the increases were transient and blood pressure returned to baseline levels during the observation periods without medical intervention. The increases also amounted to only 10 to 30 mmHg, with the maximum reading of 100 mmHg diastolic.

Ten investigators submitted reports on a total of 337 adults and 61 children (age 12 or under) taking sustained release cough/cold capsules containing 50 mg PPA, 4 mg chlorpheniramine maleate (CPM), and 0.25 mg belladonna alkaloids. Side effects were reported in 24 (7 percent) of adult patients, including drowsiness (11 patients), urinary retention (1 patient), and nausea (1 patient). There were no reports of elevated blood pressure. No side effects were reported among the children treated.

Two hundred fifty patients were given the same 50 mg product. Side effects were reported by 64 of these patients. There were no reports of elevated blood pressure.

One hundred fifty-six patients were given the 50 mg product. Side effects reported were: dry mouth (1); headache (1); and drowsiness (2). Medication was not discontinued in any of these patients because of side effects. There were no reports of elevated blood pressure.

Twenty patients were given the 50 mg product. Side effects included: drowsiness (1); increased eye itching and congestion (1); "burnt taste in stomach" (1); nosebleed (1). Medication was not discontinued in any of these patients. There were no reports of elevated blood pressure.

In a comparative study of this product and a product containing APAP 195 mg, pyrilamine maleate 25 mg, caffeine 15 mg, ephedrine sulfate 8 mg, and phenylpropanolamine hydrochloride 25 mg, 25 patients took the 50 mg PPA product and 23 took the 25 mg PPA product. Side effects were noted. There were no reports of elevated blood pressure.

One hundred eighty-eight patients were given twice daily sustained release cough/cold capsules containing 50 mg PPA, 4 mg CPM, and 0.25 mg belladonna alkaloids. Side effects were observed in 13 of the patients studied. Dryness of mouth - a reaction to the belladonnas - was reported by five patients. Upset stomach occurred in a patient being treated for ulcer symptoms. Two patients reported "jitteriness" and "irritability" and had the drug discontinued. One case of urinary retention developed in an elderly male (age 72). There were no reports of elevated blood pressure.

In another study, 111 patients were given the same 50 mg product twice daily. Dry mouth was noted in two of the patients. No other adverse effects were noted.

Eighty patients were given the same product twice daily for a period of two to six days. Side effects noted were: drowsiness (10); dry mouth (4); urinary retention (1); and nausea (1). There were no reports of elevated blood pressure.

Eighty-four patients were given the same product twice daily for one to 14 days. There was one report of dry mouth and no reports of elevated blood pressure.

Thirty-six patients took the same product. No side effects were reported.

Eighty-eight patients were given the same product twice daily. There were no adverse effects noted.

Fifteen normal volunteers received the same product for a period of six months. Pre-drug data were collected two weeks prior to dosing and one week prior to dosing. Dosage was one capsule twice daily. Two volunteers did not complete the study, for non-medical reasons. There was no control group. Results of this study showed that the product was safe for long-term use. Side effects noted were: blurring of vision (1) and abnormal SGOT, probably due to low-grade hepatitis (1). Diastolic blood pressure averages remained uniform throughout the study. Systolic blood pressure averages showed a slight increase (at Weeks 12, 13 and 20), though the mean systolic pressure was 126.5 mmHg. At Week 28, mean blood pressure was 120.5/75 mmHg. Pulse rate dropped early in the study, although this decrease did not coincide with the systolic blood pressure change. It was felt that all of the changes seen could be related to the volunteers' activities during different phases of the study.

In a three-year study evaluating the same 50 mg product versus placebo, 450 patients participated. Of the patients taking the medication, 11.5 percent developed possible side effects. Of the patients taking placebo, 8.2 percent experienced possible adverse effects. There were, however, no reports of elevated blood pressure.

A double-blind study of 178 patients with symptoms of acute coryza was undertaken comparing the effects of a product containing phenylpropanolamine HCl 75 mg and chlorpheniramine maleate 8 mg, in a sustained-release capsule; a sustained release product containing PPA 50 mg, CPM 4 mg, and belladonna alkaloids 0.25 mg; and placebo. Adverse reactions were reported by 10 percent of the patients taking the 75 mg PPA product, 12 percent taking the 50 mg PPA product, and 9 percent taking placebo. There were no reports of elevated blood pressure.

L.B. Cobin reported that mean blood pressure and pulse rates were not affected by 50 mg SR PPA (bid), 0.2 mg belladonna alkaloids (bid), a combination of the above, or placebo in 20 normal volunteers.

Dr. Richard Mulberger found no reports of elevated blood pressure during a crossover study on the comparison of placebo and a sustained release product containing PPA 50 mg, CPM 4 mg, and belladonna alkaloids 0.25 mg on intraocular pressure in normal glaucoma patients.

J. Colemore conducted an open study using 10 volunteers who received 75 mg PPA (bid, SA) for 8 weeks. No clinically significant blood pressure or pulse effects were seen. (NDA 12-685, OTC Vol. 040012.)

H. Maibach conducted an open study using 15 volunteers who received 50 mg PPA (bid, SA) for 6 months. No clinically significant changes were seen in blood pressure or pulse values. Slight increases in systolic blood pressure were seen in Weeks 12, 13, 18 and 19. (NDA 12-685, OTC Vol 040012.)

An open, crossover bioavailability study of 150 mg phenylpropanolamine (od, SA), 75 mg phenylpropanolamine (od, IR), and 50 mg phenylpropanolamine (od, IR) was conducted, using 12 volunteers. No significant blood pressure effects were recorded. (NDA 18-099.)

b. To what extent may PPA aggravate pre-existing hypertension at the recommended dose levels?

Clinical studies demonstrate that PPA does not aggravate pre-existing hypertension.

Two clinical studies have come to this conclusion, one published and one unpublished. D.L. Unger, L. Unger and D.E. Temple reported on the "Effect of an anti-asthmatic compound on blood pressure of hypertensive asthmatic patients" in Ann. Allergy 25: 260-261, 1967. Doses of 25 mg phenylpropanolamine were given three times a day to 21 asthmatic hypertensive patients for one to three weeks. Baseline blood pressure averaged 166/102; within one hour after administration, the average blood pressure was 164/102. The median blood pressure pre-dosing was 164/104 and after dosing 168/102. Five patients had a 10 mmHg elevation in systolic blood pressure and five had a decrease of 10 mmHg. Four patients had a 10 mmHg elevation and four a 10 mmHg decrease in diastolic blood pressure. None of the patients studied had to discontinue use of phenylpropanolamine because of side effects. The authors concluded that phenylpropanolamine produced no significant changes in blood pressure at the time of peak blood levels following administration of 25 mg doses.

In a pilot, single-blind, crossover study conducted by M.H. Bradley, M.D., on ten exogenous obese patients with controlled hypertension, no clinically significant changes in blood pressure values were seen in patients who were given 25 mg PPA (tid), placebo, and 75 mg PPA (od). (See Exhibit 4.)

c. To what extent may PPA interact with aspirin and other medications that inhibit prostaglandin synthesis at the recommended dose levels?

There is abundant evidence from the long use of PPA/aspirin combinations in OTC cough/cold products that such combinations do not induce hypertension. This has been confirmed conclusively by clinical studies of aspirin alone and of aspirin in combination with phenylpropanolamine.

The agency's request for information on this question arises from a report on a single patient. Lee, Beilin, & Vandongen [Ref. 8] reported severe hypertension in a single patient taking an 85 mg dose of phenylpropanolamine together with a 25 mg dose of the non-steroidal anti-inflammatory medication, indomethacin, although neither of the drugs was associated with hypertension in the patient when given alone. The authors of this single patient report apparently postulated that the decrease in prostaglandin levels due to indomethacin concomitantly reduced the inhibitory action on catecholamine release. As a result, the administration of phenylpropanolamine may have invoked a greater than expected release of catecholamines, resulting in profound vasoconstriction and an increase in blood pressure.

The record indicates that hypertension is known to occur from the clinical use of indomethacin (A. Wennmalm, "Influence of Indomethacin on the Systematic and Pulmonary Vascular Resistance in Man," Clin. Sci. Mod. Med. 54: 141-145, 1978; 1982 Physicians Desk Referance). However, no such data is available with regard to aspirin. Furthermore, the known long-term concurrent use by patients of aspirin and phenylpropanolamine to alleviate the discomfort of the common cold has not indicated evidence of any significant hypertensive responses.

There have been several large, well-controlled studies which have examined the potential for chronically administered aspirin to influence blood pressure. No hypertensive effect of aspirin has ever been demonstrated (The Coronary Drug Project Research Group, "Aspirin in Coronary Heart Disease," J. Chron. Dis. 29: 625-642, 1976; A.A. Cooper, "Efficacy of Zomepirac in Oral Surgical Pain," J. Clin. Pharmacol. 20: 230-242, 1980).

There are a number of leading non-prescription cold and allergy products which have combined aspirin with phenylpropanolamine in addition to other ingredients (Handbook of Nonprescription Drugs, Sixth Edition, Amer. Pharm. Assoc., Washington, D.C. 1979, pp. 107-112). Many nonprescription and prescription combination products have been used safely for many years in the United States as well as in Europe. If there were any real potential for interaction between aspirin and phenylpropanolamine or any other sympathomimetic, it would certainly have been obvious. Yet the market experience has been remarkably free of adverse reactions. A consortium of cough/cold product manufacturers made a presentation to the Cough/Cold Panel on September 1, 1974, in which they submitted the following data on adverse reactions per 100,000 packages of various leading combination products:

C

Combination	Adverse Reactions Per 100,000	Total Packages Sold
PPA and acetaminophen	0.282	1 million to 10 million
PPA, chlorpheniramine, and aspirin	0.109	10 million to 50 million
PPA, chlorpheniramine and calcium carbaspirin	0.091	1 million to 10 million

This admirable record of reported adverse reactions over the years of use of these products indicates how remote is the possibility of significant occurrence of the adverse reaction in question.

Clinical evidence that a therapeutic interaction between aspirin and PPA does not occur is well demonstrated in a 30-day human study. (Cough, Cold, Asthma, Bronchodilator and Allergy Panel Report, F.R. Sept. 9, 1976; OTC Volume 040298 (1971)). This double-blind, clinical trial employed a total patient population of 68 (65 male; 3 female), and included four identical-appearing tablets of different composition provided to subjects by random assignment. Dosage was two tablets taken 4 times daily.

Formula Code	Composition per tablet	Total Daily Dose
SHP-78	ASA-325 mg PPA- 25 mg	2600 mg 200 mg
SHP-79	PPA- 25 mg	200 mg
SHP-80	ASA-325 mg	2600 mg
SHP-82	Placebo	

A total of 26 patients completed 30 days on the complete regimen using SHP-78 while three other groups of nine patients per group completed the 30-day therapy using the other three dosage forms. Subjects not consuming the assigned dosages were dropped from the study.

Formula Code	SHP-78	SHP-79	SHP-80	SHP-82
Subjects Assigned	34	11	11	12
Subjects Dropped	8	2	2	3
Subjects Completed	26	9	9	9

All subjects were provided with clinical and laboratory evaluations including blood chemistry, urinalysis, blood count, blood pressure, pulse rates, body weights, and oral temperatures. Pulse and blood pressure were monitored on Days 0 (day prior to administration), 7, 15, 22 and 30. One patient in the ASA group exhibited a dramatic increase in pulse rate on Day 30. This was attributed to personal problems on that day specifically and was not considered to be drug-related. The conclusion reached upon completion of the study was that no evidence of drug-related toxicity was observed or determined.

This study therefore provides conclusive evidence of a lack of interaction between PPA and aspirin. Additionally, it provides further support for the proposition that PPA does not adversely affect blood pressure. Subjects in this study ingested a total of 200 mg PPA daily for 30 days in individual 50 mg doses. Tablets were not sustained release. A total of 35 subjects completed the 30-day regimen taking PPA. On the basis of the dosage employed, the number of subjects enrolled, and the length of time they received a combination of PPA with the non-steroidal anti-inflamatory product aspirin, no adverse effects relative to blood pressure or other vital signs were reported.

Summary

The data that was before the Panel, and the more extensive data which has become available since the Panel completed its work, constitutes a massive amount of scientific evidence drawn from 60 controlled clinical studies involving more than 3,700 patients. This data demonstrates that PPA does not induce hypertension either in normotensives or hypertensives or when it is in combination with aspirin. This data, together with almost 50 years of safe use of PPA in this country, clearly outweighs the handful of adverse reports referred to in the agency's Preamble.

2. The Proprietary Association recommends that the FDA accept the Panel's recommendation with regard to labeling for the combination of phenylpropanolamine hydrochloride and caffeine.

The Panel Report recommends Category I status for the combination of phenylpropanolamine hydrochloride and caffeine if labeled as an "Anorectic/Stimulant" (page 8476, first column). In its preamble FDA invites comment on alternate or consolidated label warnings and directions for such combinations, noting that a discrepancy exists between the directions for use of caffeine in this and another current proposal to the agency (page 8469, first column).

The warning proposed in the Tentative Final Monograph of the Panel on Over-The-Counter Nighttime Sleep-Aid and Stimulant Products (Sleep-Aid Panel) was, "For occasional use only." (§ 340.50(c)(2); 43 F.R. 25602). However, the warning proposed by the Miscellaneous Internal Panel for Weight Control Products specified daily doses for up to three months. (§ 357.550(d); page 8484, second column).

We do not believe the agency's concern about this discrepancy is warranted. Caffeine in combination with phenylpropanolamine hydrochloride in weight control products is intended only as adjunctive therapy, used to mitigate the lethargy that may accompany a reduced diet regimen. As the Panel Report stated,

> ". . . the Panel had to decide whether or not a significant portion of the dieting population becomes fatigued while dieting. Based upon its professional experience the Panel concluded that such a significant patient population does exist and that the combination of phenylpropanolamine hydrochloride and caffeine meets the three criteria of FDA's combination policy." (Page 8476, first and second columns).

By contrast, caffeine in stimulant products is intended to "help restore mental alertness or wakefulness during fatigue or drowsiness" whenever these conditions occur. (§ 340.3; 43 F.R. 25602).

In addition, the quantity of caffeine in the weight control products is inherently limited to 600 mg per day by the current and recommended maximum frequency of dosage of three times a day. Again, by contrast, when caffeine is used as a stimulant product, the recommended maximum dosage can be as much as 1200 mg per day (100 to 200 mg not more often than every 3 to 4 hours).

Therefore, it is appropriate to require the more restrictive warning on the caffeine products for relief of general fatigue and drowsiness.

Moreover, the amount of caffeine involved in combination with phenylpropanolamine hydrochloride in the weight control products is 100 to 200 mg. It is essential to note that this is only the equivalent of approximately two cups of coffee. In these dosages, caffeine has been found to be safe, either alone or in combination with other substances, by three other OTC advisory panel reports, in addition to the Weight Control Products Panel Report. The most recent of these other panel reports, on Orally-Administered Menstrual Drug Products, summarized all three panel reports as follows:

> "(2) Caffeine. The Panel concludes that caffeine is generally recognized as a safe and effective diuretic for OTC use in the doses noted below in relieving water accumulation symptoms of the premenstrual and menstrual perod.
>
> "(i) Safety. The toxicity of caffeine has been reviewed extensively by the Advisory Review Panel on OTC Sedative, Tranquilizer, and Sleep Aid Drug Products in a report published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). That Panel discussed, in addition, the mutagenic effects of caffeine in detail. It found caffeine to be safe ". . . when used in the recommended oral dose of 100 to 200 milligrams (mg) not more often than every 3 to 4 hours." FDA concurred with the Panel in the tentative final monograph published in the FEDERAL REGISTER of June 13, 1978 (43 FR 25544).
>
> "The Internal Analgesic Panel also reviewed caffeine for its analgesic properties in the FEDERAL REGISTER of July 8, 1977 (42 FR 35346) and expressed its agreement with the conclusions of the Advisory Review Panel on OTC Sedative, Tranquilizers and Sleep Aid Drug Products regarding the safety of caffeine. This Panel

> agrees with the above reports and concludes that caffeine is safe as an OTC diuretic for relieving water accumulation symptoms of the premenstrual and menstrual period in doses of 100 to 200 mg every three to four hours." Second Information Copy, OTC Orally Administered Menstrual Drug Products Report, September 22, 1981, pp. 55-56.

In its final meeting on October 15-17, 1981, the Panel, in its review of the Menstrual Drug Products Report, added to this conclusion its approval of a combination of caffeine with a menstrual product. Moreover, it did so based on the same rationale it used for its approval of the combination of phenylpropanolamine and caffeine in weight control products, that is, relief of fatigue. The minutes of the Panel meeting state:

> "The Panel was made aware that caffeine is contained in an OTC menstrual drug product (a combination product) which contains a claim for the relief of fatigue in the premenstrual period. Because the Panel has already recognized that fatigue is a component of the premenstrual syndrome and because caffeine has already been classified as a Category I stimulant by another panel, this Panel concludes that caffeine is an effective menstrual drug product ingredient for the claim of relieving fatigue occurring in the premenstrual period." Summary Minutes of the Forty-Sixth Meeting of the OTC Miscellaneous Internal Drug Products Panel, October 15-17, 1981, p. 5.

Finally, it is noteworthy that even in FDA's current inquiry regarding the use of caffeine as an added food ingredient, the agency has specifically exempted from that inquiry the presence of caffeine in coffee and the use of caffeine in drugs.

3. The Association disagrees with the Panel's conclusion that vitamins and minerals should not be constituents of weight control drug products.

The Panel report notes that some weight control products now on the market contain a number of vitamins and minerals in addition to their weight control active ingredients. The Panel also states its belief that it is the responsibility of the consumer "to determine the dietary regimen to follow in order to maintain a well-balanced, low-caloric diet" (page 8472, third column).

We share the Panel's belief in this regard. However, we strongly disagree with the Panel's conclusion which is purportedly based upon this belief. The Panel somehow leaps from its belief about a well-balanced diet to the conclusion that "therefore, the addition of vitamins and minerals [in combination with the weight control active ingredients] serves no useful purpose for those following a well-balanced diet" and "vitamins and minerals should not be constituents of weight control drug products" (id.).

The Panel's conclusion does not follow logically from its premise and also conflicts with one of the Panel's other recommendations, which FDA strongly endorses in the preamble, that "a reduction in total daily caloric intake below the energy output" must accompany weight control drug products in order to achieve significant weight loss (page 8468, third column; page 8469, first column; page 8472, second and third columns). Again, we agree with this recommendation.

However, a consumer who follows this label direction and reduces caloric intake below the energy output may, no matter how well-balanced the resultant diet, also reduce the amount of vitamins and minerals previously needed to maintain the consumer's body weight and frame. The recommended dietary intake of essential nutrients, particularly vitamins and minerals, may be difficult to achieve during caloric reduction, since in many foods vitamins and minerals are present only in low concentrations. Under these circumstances it may be desirable to provide the consumer with the option of obtaining a vitamin and mineral supplement in combination with phenylpropanolamine hydrochloride appetite suppressant in order to replace those vitamins and minerals lost as a result of lowering food intake.

Finally, vitamins and minerals which are dietary supplements are foods and should be treated as such in this combination. Combinations of cosmetics and drugs are permitted so long as each complies with applicable regulations. The same rule should be applied to the combination of vitamins and minerals with weight control active ingredients. The Bureau of Drugs should impose no more stringent requirements on such a vitamin and mineral supplement than does the Bureau of Foods.

It is in the best interest of good medicine and of the consumer to make generally available the greatest possible variety of safe and effective medication. Manufacturers should therefore not be prohibited, contrary to the Panel's recommendation, from offering such a rational combination of PPA and vitamins and minerals.

4. The Proprietary Association recommends that the FDA reject some of the Panel's recommendations with regard to Category II labeling.

The Association recommends that the following claims recommended by the Panel to be placed in Category II should instead be placed in Category I. We believe that some of these claims represent the same claims which the Panel recommended be placed in Category I but are stated in language that is more readily understood by the consumer. Others are truthful statements or, at most, amount to acceptable puffery. Indeed, the Panel itself stated that it "is aware that there may be other terms that would be acceptable in expressing the same Category I indications" (page 8473, first column).

These thirteen statements should not be classified in Category II because they do not, in fact, lead to use of the product other than in the manner recommended by the Panel as generally recognized as safe and effective. Each of these Category II claims is discussed below:

a. "Contains one of the most powerful diet aids available without prescription" (page 8476, second column). This is a true statement. The Panel recommended only two substances - - phenylpropanolamine hydrochloride and benzocaine - - for Category I as safe and effective.

b. "Contains one of the strongest diet aids available without prescription" (id.). Like claim "a", this is a true statement for products containing phenylpropanolamine.

c. "Encourages water loss with a gentle diuretic" (id.). This is a true statement for products containing caffeine. Caffeine has been recommended for Category I as a diuretic by the panel reviewing orally-administered menstrual drug products and in Category I as a mild stimulant by both the Nighttime Sleep-Aid and Stimulant Products Panel and the panel reviewing menstrual drug products. A fuller discussion appears above on pp. 17-19 in section 2 relating to the labeling for caffeine/phenylpropanolamine combinations.

d. "Easy-to-follow reducing plan built around food you love to eat. You will eat well but less and lose weight without going hungry" (*id.*). Clinical studies submitted to the Panel demonstrate weight loss where caloric intake has been reduced in accordance with diet plans recommended along with these products. These diet plans contain a wide variety of nutritious foods, limited only in quantities, not in the breadth of the array of foods specified. This labeling should certainly be allowed on products which are packaged with a diet plan.

e. "A unique way to help your overweight patient eat less" (*id.*). This is a true statement because these products *involve* the consumer's using a specific, approved medication to reduce appetite, rather than requiring the consumer to simply try to follow exhortations to reduce calories without the assistance of medication.

g. "Now enjoy a slim, trim figure. Lose pounds. Reduce inches" (page 8476, third column). These claims are lay descriptions of goal-oriented products and are helpful in encouraging proper compliance with product instructions.

h. "Lose weight starting today. Look your best, feel your best" (*id.*). This is a true statement. When caloric intake *is* reduced below energy requirements, the body begins to use up stored fat for energy. The claim does not refer to any specific amount of weight loss on the first day. While the amount may be relatively small, it is nonetheless a start and, once the process starts, the end result is closer than before. Like claim "g," these claims are lay descriptions of those goals and are helpful in assuring proper compliance with product instructions.

i. "The delightful aid to appetite control" (*id.*). Except for "delightful" this is the same as "An aid *in* the control of appetite," recommended for Category I by the Panel (page 8476, first column, ¶ 2(6)). The addition of "delightful" is harmless puffery, fully justified by the fact that the recommended diet plans enclosed with the products contain a broad array of foods. The reasoning for this is the same as for claim "d" above.

j. "Delightfully delicious, scientifically formulated to help you control your appetite quickly, pleasantly" (page 8476, second column). As in the case of claim "i", above, the addition of "delightfully delicious" is, again, justified by the breadth of variety in the foods included in the diet plans enclosed with these products. The phrase "scientifically formulated" is truthful.

k. "A most pleasant aid to help you lose weight" (id.). As in the case of claims "d", "i" and "j", above, the phrase "most pleasant" is fully justified by the wide variety of foods permitted by the diet plans enclosed with the products.

l. "Trim pounds and inches without crash diets and strenuous exercise" (id.). This is a true statement and is also properly goal-oriented, like claims "g" and "h."

m. "A modern aid to appetite control for people who love to eat" (id.). This accurately describes in lay terms the target population of those who, without this aid, would eat larger quantities of food.

o. "Reduce to the weight and size you want to be" (id.). As in the case of claims "g," "h," and "l," it is important in ensuring proper compliance with product instructions for the consumer to keep the goals in mind.

q. "An effective easy-to-follow diet plan that lets you enjoy eating delicious nutritious foods everyday as you lose weight" (id.). Like claim "d," this is a truthful statement.

r. "Enables the obese individual to lose weight in the most comfortable manner by decreasing the desire for food" (id.). These products enable obese individuals to lose weight "in the most comfortable manner" because appetite is reduced for greater quantities of food than permitted by the enclosed diet plans.

s. "Hunger pains are spared and a low calorie reducing diet may now be more easily tolerated" (id.). This is a truthful statement, describing accurately the process by which these products achieve results.

Claims "r" and "s" are not only truthful but describe in detail the manner in which the product works. In fact, these statements clearly explain to the consumer the reasons for the Panel's proposed statement: "This product's effectiveness is directly related to the degree to which you reduce your usual food intake" (page 8475, first column).

CONCLUSION

The Association supports the Panel's classification of phenylpropanolamine hydrochloride as generally recognized as safe and effective when used in OTC weight control products. The extensive data discussed above demonstrate the safety of phenylpropanolamine at the 150 mg daily dosage level and amply support the safety of the currently-marketed weight control products at the 75 mg daily dosage level. The Association also supports the Panel's recommendation that the combination of phenylpropanolamine and caffeine is safe and effective if labeled as an "anorectic/stimulant."

The Association believes that weight control active ingredients in combination with vitamin and mineral supplements should be allowed, contrary to the Panel's recommendation. In addition the Association urges that FDA reject some of the Panel's recomendations with regard to Category II labeling.

The Association appreciates the opportunity to submit these comments and hopes that the agency finds them helpful.

Sincerely,

THE PROPRIETARY ASSOCIATION

Jim Cope

James D. Cope
President

EXHIBIT 1

"Comparison of the Anorectic Activity of Prolamine and Placebo Without Concomitant Nutritionally Balanced Diet." Marianne Sebok, M.D., Staff Physician, JFK Memorial Hospital, Philadelphia, PA. A double-blind six week clinical evaluation was conducted with 72 patients who received either 35 mg phenylpropanolamine and 140 mg caffeine (sustained release) or a placebo twice a day. Throughout the study, no clinically significant variations at sitting blood pressure or pulse were observed or reported. PPA patients lost statistically significant amounts of weight compared with placebo patients.

"Double-Blind Evaluation of Phenylpropanolamine-Caffeine Product as an Adjunct in the Treatment of Obesity." E. R. Jolly, M.D., BioMetrics Laboratory, Clifton, NJ. Findings: A double-blind 12-week study of 63 patients revealed that 21 patients on phenylpropanolamine-caffeine showed an average weight loss of 15 pounds, and 13 patients on placebo showed a weight loss of 8 pounds over the 12-week test period, or 1.2 pounds per week for the phenylpropanolamine patients compared to .66 pounds per week for the placebo patients. Side effects were minimal and equally divided amoung placebo and active drug groups. One patient on the active medication reported hyperstimulation and sleeplessness and one patient on the placebo noted extreme nervousness. No significant changes in blood pressure or pulse rate were observed.

"Double-Blind Clinical Evaluation of the Anorectic Activity of Phenylpropanolamine Alone Compared to Phenylpropanolamine Plus Caffeine in the Treatment of Outpatients with Exogenous Obesity." Anthony Conte, M.D., Pittsburgh, PA. In an 8-week double-blind randomized clinical test, phenylpropanolamine 50 mg was compared to phenylpropanolamine 50 mg with caffeine 200 mg (sustained release.) Of the sixty-two obese adults who entered the clinical evaluation, both groups lost similar amounts of weight. No deviations from baseline were reported in sitting blood pressure (systolic/diastolic) or pulse.

In an open, crossover comparative study, the bioavailability of 25 mg phenylpropanolamine (q4h, IR), 75 mg (od, IR) and 75 mg (od, SA) was tested in 18 volunteers by Donald Flaster, M.D. No significant blood pressure effects were reported.

Griboff, et al., reporting in Current Therapeutic Research 17: 535-43, 1975, found no significant changes in blood pressure or pulse measurements in a double-blind parallel study on 66 volunteers receiving 25 mg PPA with 100 mg caffeine (tid) or placebo. PPA patients lost significant amounts of weight compared with placebo patients.

Altschuler, Sebok and Conte conducted 6-8 week, double-blind, parallel studies using 50 mg PPA (od, SR), 37.5 mg PPA (bid, SR), and 25 mg PPA (tid, IR), respectively. No significant effects on blood pressure or pulse rate were reported or observed. Significant weight loss was reported.

In a double-blind, crossover study conducted by Bartley G. Hoebel, Ph.D., et al., at Princeton University, Princeton, NJ, phenylpropanolamine (25 mg, tid) reduced body weight in 70 adults significantly more than a placebo pill. During the first two weeks both the subjects taking the placebo and those taking phenylpropanolamine lost weight, but during the second two weeks only those taking the drug continued to lose. On daily questionnaires those taking the drug reported no change in the way they felt or the time it took to fall asleep.

F. B. Bohensky, M.D., Brooklyn, New York, conducted a single-blind, four-week, crossover clinical evaluation of 60 patients in Dr. Bohensky's private offices. Appedrine (25 mg phenylpropanolamine plus 100 mg caffeine plus multivitamins, tid) was compared to dextro-amphetamine and placebo as an appetitie suppressant. The results indicated that the phenylpropanolamine group (Appedrine) on the average lost 1.98 pounds per week, the dextro-amphetamine group on the average lost 2.3 pounds per week, and the placebo group on the average lost .62 pounds per week. No significant changes in blood pressure or mood changes were reported or observed.

Exhibit 2

Massachusetts College of Pharmacy
and Allied Health Sciences

September 25, 1981

J. Richard Crout, MD, Director
Bureau of Drugs, HFD-1
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Crout:

This letter is in follow-up to our discussions on sustained action dosage forms and your interest in the physiological response to a 75 mg bolus dose of phenylpropanolamine HCl. You will recall, I'm sure, our meeting on September 11th in the Commissioner's office at which time we reviewed the F.R. publication status of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products - Proposed Monograph for OTC weight control drug products.

As an avid student of the sustained action dosage form and phenylpropanolamine, I was certain, as I advised you at the meeting, that my files included descriptions of experimental work where a 75 mg bolus of PPA had been administered to human volunteers in a plain immediate release dosage form and the hemodynamic response studied. The SBA for NDA 18-099, "Contac" provides information describing a three way cross-over study employing twelve normal human volunteers. The three dosage regimens were:

(A) Two "Contac" sustained action capsules containing 75 mg PPA and 8 mg CPM per capsule.

(B) 75 mg PPA and 8 mg CPM, plain drug as a bolus dose.

(C) 50 mg PPA and 5.33 mg CPM, plain drug at 0, 4 and 8 hours.

The bioavailability study determined plasma levels at the 1, 2, 3, 4, 6, 8, 10, 12 and 24 hour periods following drug ingestion. In addition, blood pressure and pulse (supine and standing) were taken

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Reproduced by The Proprietary Association 7/16/82 before and at 1, 5 and 11 hours after drug dosing. No clinically significant change in blood pressure or pulse in any volunteer during the study was reported. I might add this information is especially important in view of the report by Horowitz, et al "Hypertensive Responses Induced by Phenylpropanolamine in Anorectic and Decongestant Preparations", Lancet, 1980; 1:60-61. The Horowitz study would suggest one might expect an increase in supine diastolic blood pressures in some volunteers ingesting ≥ 75 mg PPA bolus, inasmuch as the dose of PPA in the Australian study was reported to be 85 mg, only 10 mg greater. However, no clinically significant changes in blood pressure are reported in the carefully controlled study submitted in support of NDA 18-099.

At the time of our own studies, ("Lack of Side Effects from Orally Administered Phenylpropanolamine and Phenylpropanolamine with Caffeine: A Controlled Three-Phase Study", Current Therapeutic Research 20, 135-194; 1980) we received a small number of the Australian product "Trimolets" for evaluation. "Trimolets" was the 85 mg PPA product reported on in the Horowitz paper. The capsules contained a fine yellow powder labelled to contain D-phenylpropanolamine 85 mg plus ferrous gluconate, calcium pantothenate, thiamine, riboflavin, pyridoxine and nicotinamide. Only three capsules were received assaying out at 82.2 mg, 79.7 mg and 83.5 mg respectively (average 81.8 mg). The PPA in these capsules was immediately soluble in water, and not in a sustained release form.

Regarding the integrity of the sustained release dosage form marketed in this country, I would like to add that our laboratories have, for years now, evaluated hundreds of pelletized sustained release PPA dosage forms marketed by the Thompson Medical Company. Our laboratories provide a periodic quality control audit and assurance function for Thompson as a further check to insure compliance of manufactured dosage forms with product specifications. I am pleased to indicate we have never encountered a product where "dose-dumping" under in vitro testing occurred and the sustained release character of a dosage form was compromised. The number of safety and quality control steps taken, prior to batch release, assure safety and efficacy of the sustained action product and provides an exceptional degree of quality assurance ruling out any possibility of the occurrence of "dose-dumping." Clinical bioavailability studies have provided assurance of the effectiveness of the timed-release activity with excellent correlation between a single dose of the timed-release formulation (75 mg) and three doses of the immediate release dosage form (25 mg) taken at 4 hour intervals. Hence, ongoing in vitro quality control, in our experience, assures product performance on a level consistent with the in vivo results.

Thompson's 75 mg timed-release PPA dosage forms are manufactured to conform with the following in vitro dissolution pattern limits.

Hour	% Release	mg Release
1	30 - 45	22.5 - 33.75
4	50 - 75	37.5 - 56.25
8	80 - 100	60 - 75

The dissolution pattern is developed by sampling at 1, 2, 4, 6 and 8 hours.

I trust these comments are a helpful sequel to our earlier discussion and provide some assistance to you.

Sincerely,

PFEIFFER PHARMACEUTICAL
SCIENCES LABORATORIES

H. I. Silverman

H.I. Silverman, D.Sc.
Professor and Executive Director

HIS/lf

cc: Mrs. Barbara Bayer
Marion J. Finkel, MD
William E. Gilbertson, Pharm.D.
Judith K. Jones, Ph.D.
Mark Novitch, MD
Dr. Edward Steinberg

Exhibit 3

of system involvement and with presentation either in childhood or in adulthood, treatment would generally be in conjunction with other specialists. Seeing patients together in combined clinics would seem to be the best way of achieving this.

There is an air of defeatism related to many lethal or seriously handicapping genetic disorders. Clinical geneticists must not encourage this by being satisfied to limit their involvement to diagnosis and genetic counselling.

Royal Manchester Children's Hospital,
Manchester M27 [illegible]

M. Super

PHENYLPROPANOLAMINE AND BLOOD PRESSURE

SIR,—Although phenylpropanolamine (PPA) has been safely used in the U.S.A. for over forty years as a nasal decongestant, your April 10 editorial raised the possibility that PPA in weight control preparations could produce increased blood pressure.

In the past two years, I have done three large studies in our obesity clinic in San Francisco of the effects of three dosage forms of PPA. More than 400 obese patients were studied. The results will be published elsewhere.

Data were gathered on a twelve-week, double-blind, placebo controlled study of 50 mg PPA three times daily (twice the recommended dose for weight loss); a double-blind, placebo controlled study of 50 mg PPA combined with 200 mg caffeine in controlled-release form; and a single-blind trial of 75 mg PPA in controlled-release form.

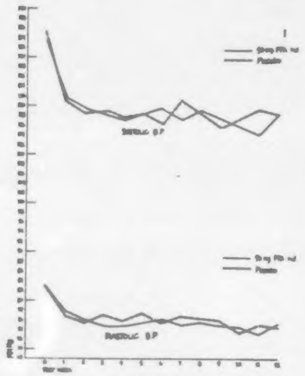
All three dosages caused no significant increase in blood pressure in more than 400 patients. 2 patients experienced noteworthy rises in blood pressure after treatment with 75 mg PPA, but these increases were felt not to be drug related.

The mean pooled systolic and diastolic blood pressure in the 50 mg × 3 PPA/placebo study are shown in the figure.

Our results confirm that PPA does not cause a significant increase in blood pressure even when the amount ingested (150 mg/day) is substantially higher than the recommended 75 mg dose. There was, on the contrary, a reduction in blood pressure as the studies progressed.

Cathedral Hill Obesity Clinic,
San Francisco, California 94103, U.S.A.

RUDOLF E. NOBLE



Mean systolic and diastolic blood pressure.

CEFTAZIDIME AND SALMONELLA

SIR,—Dr Gozzard and colleagues (May 22, p. 1152) listed a *Salmonella newport* septicaemia treated with ceftazidime 1 g three times daily as a failure. The minimum inhibitory concentration for that strain was 0·25 μg/ml. Probably the dosage was too low. We have treated a 33-year-old African man, who had sickle cell anaemia and an osteomyelitis with *S. typhimurium* (MIC 0·25 μg/ml), successfully with, at first, 2 g twice daily for 17 days and, after an operation, 3 g twice daily for 25 days. The bone marrow sample taken during operation was sterile. A higher dosage is probably required in *Salmonella* (and, possibly, *Shigella*) infections. Of interest would be information on susceptibility of the isolated organisms to other currently available antibiotics and successful treatment of the infections by ceftazidime, where prior antibiotic therapy had failed.

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West Germany

PRAMOD M. SHAH
WOLFGANG STILLE

MYOCARDIAL CARNITINE DEFICIENCY IN ACUTE MYOCARDIAL INFARCTION

SIR,—Dr Suzuki and colleagues (Jan. 9, p. 116) reported decreased levels of free L-carnitine in the myocardium of chronic heart failure patients and a concomitant rise in acylcarnitine. These changes are related to a removal of accumulated free fatty acid (FFA) and long-chain acyl-CoA esters secondary to chronic hypoxia which in turn inhibits adenine nucleotide translocase.[1] This metabolic device, also observed in dog hearts during the reversible phase of ischaemia[2] seems to act as a servo mechanism tending to relieve myocardial injury. Suzuki et al. suggested the administration of exogenous L-carnitine during acute and chronic cardiac ischaemia. In acute experimental ischaemia, however, progressively more total L-carnitine is lost the longer the ischaemia lasts.[2] The two findings strongly suggest that the maintenance of physiological levels of L-carnitine and the acylcarnitine to free carnitine ratio play an important role in the control of the metabolism of the injured myocardium.

We measured[3,4] heart L-carnitine levels at necropsy in seven patients who had had acute myocardial infarctions and in four who had died from causes other than heart disease. In the first group the tissue samples were removed from the necrotic area, from the border zone, and from the healthy myocardium; whereas in the controls L-carnitine levels were separately determined in specimens taken from the left ventricular walls. The necrotic myocardial areas had lower L-carnitine levels, while the border zone tissue showed intermediate values between necrotic and healthy surrounding tissue levels. There was no discrepancy between the myocardial L-carnitine values in the controls and those found in the healthy surrounding tissue of those who had died from myocardial infarction.

We did not observe short and long chain carnitine esters in the tissue fragments of either group, presumably because in specimens removed 24 h after death all the L-carnitine content is present in the free isomer form, as a result of hydrolysis during the period since death and during storage at −25°C for 10–15 days. Therefore, in our experimental model free L-carnitine corresponds to total carnitine. This statement is supported by the fact that the tissue L-carnitine levels we found in the healthy myocardium were identical to the total L-carnitine levels measured by Cederblad in the myocardium of heart surgery patients.[5]

---

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Exhibit 4

THOMPSON MEDICAL COMPANY, INC.
919 THIRD AVENUE • NEW YORK, N.Y. 10022 • (212) 688-4420

PROGRESS REPORT ON THE PILOT STUDY "DOUBLE-BLIND SAFETY AND EFFICACY EVALUATION OF PHENYLPROPANOLAMINE HCl IN EXOGENOUS OBESE PATIENTS WITH CONTROLLED HYPERTENSION"

Chief Investigator:

Matthew H. Bradley, M.D.
1160 Kane Course
Miami, FL 33134

Submitted to:

Thompson Medical Company, Inc.

July 16, 1982

Prepared by:

K.M. Farragher

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    - c. Intraweekly Treatment Value Comparisons
  - 2. Laboratory Blood Analysis Data
    - a. Biweekly Treatment Value Comparisons
    - b. Biweekly Laboratory Values
  - 3. Laboratory Oral Temperature Data
- C. Weight Loss Data (Efficacy Analysis)
- D. Side Effects

VII. CONCLUSIONS

I. STUDY PURPOSE

The purpose of this study is to evaluate the efficacy, tolerance, and safety of phenylpropanolamine HCl (PPA) vs placebo in the treatment of exogenous obesity in patients with controlled, stable hypertensive diseases.

II. PATIENT POPULATION PROFILE

The patient population profile included twelve (12) patients in the age range of 25 to 67 years with exogenous obesity and controlled, stable hypertensive disease.

A controlled, stable hypertensive disease was defined as diastolic blood pressure at or below 94mmHg. The hypertensive disease state was controlled with thiazide, with and without concomitant potassium supplements.

Exogenous obesity was defined as at least 10%, but not more than 55% overweight as calculated using the revised Metropolitant Life Insurance Company Statistical Book 47:1, 1966.

III. PATIENT EXCLUSION CRITERIA

1. Patients currently using concommitant medication which would interfere with the evaluation of safety and/or efficacy, i.e. MAO inhibitors.
2. Patients who have suffered a recent (3-6 months) myocardial infarction or with severe cardiac decompensation.
3. Patients who have had recent (3-6 months) surgery.
4. Patients with elevated venous blood pressure.
5. Patients with unstable or accelerated anginal episodes.
6. Patients who exhibit complications of hypertenstion or arteriosclerotic cardiovascular disease, such as cerebral ischemia or uremia.
7. Patients who cannot adhere to the protocol visit schedule.
8. Patients who are pregnant or lactating.
9. Patients who have been on weight reduction programs or medication during the three weeks prior to this study's initiation.

IV. STUDY DESIGN

The study was a single-blind crossover study which extended for six weeks according to the following medication and dosage schedule:

WEEK 1 & WEEK 2	Phenylpropanolamine 25 mg. caffeine 100 mg t.i.d. (one hour before meals)

IV. STUDY DESIGN (continued)

WEEK 3 & WEEK 4	Placebo, b.i.d. (10 a.m. & 4 p.m.); washout period
WEEK 5 & WEEK 6	Phenylpropanolamine 75 mg. o.d. (10 a.m.)

Data was collected according to the following schedule:

INITIAL VISIT (Day 0).............Chest X-Ray, Background & Clinical Data

WEEKLY VISITS.....................Body Weight, Vital Signs (oral temperature, blood pressure, pulse), Appetite Suppression (degree, duration), Side Effects

BIWEEKLY VISITS..................Physical Examination, Supine Electrocardiograph Tracing, Blood Pressure and Pulse ½,1,2 & 4 hours after initial dose.

V. STATISTICAL METHODS

Analysis of variance (t-tests) was performed on the differences between baseline values and (a) biweekly treatment group values and (b) biweekly treatment group values taken at ½, 1, 2, and 4 hours for blood pressure and pulse measurements.

These variables were also tested for significant differences for each treatment group during each treatment week (i.e., weeks 1 vs 2, week 3 vs 4, week 5 vs 6).

Laboratory values (glucose, triglycerides, cholesterol, GGTP, SGOT, LDH, sodium, potassium, chloride and oral temperatures) were compared for significiant differences between baseline and end of treatment group values. Also, laboratory values for placebo vs medicated treatments were compared.

Hunger feelings (appetite suppression) and weight loss measurements were examined for differences between baseline and end of treatment group values.

A 95% confidence level was used to test the statistical significance of the data.

VI. STUDY RESULTS

A. PATIENT POPULATION PROFILE

Ten of the initial twelve patients completed the study. Patients #4 and #10 completed the first crossover leg but were discontinued because of protocol violations (using an MAO inhibitor and previous time commitments, respectively). Neither patient reported any adverse reactions.

Table #1 presents the patient population profile in terms of age, sex and weight/height characteristics.

TABLE #1: PATIENT POPULATION PROFILE

	PATIENTS ENTERED	PATIENTS COMPLETED
NUMBER	12	10
SEX		
Male	3	2
Female	9	8
AGE (YRS)		
Mean	54.5	54.4
Range	25-67	25-67
BODY FRAME		
Small	0	0
Medium	7	7
Large	5	3
% OVERWEIGHT		
Mean	26.6%	23.8%
Range	12-54	12-54
INITIAL WEIGHT		
Mean	184.7	173.8
Range	149-284	149-284
IDEAL WEIGHT		
Mean	139.9	137.2
Range	125-184	125-184

B. VITAL SIGNS DATA

1. Blood Pressure and Pulse Data

a. Baseline vs Biweekly Treatment Values

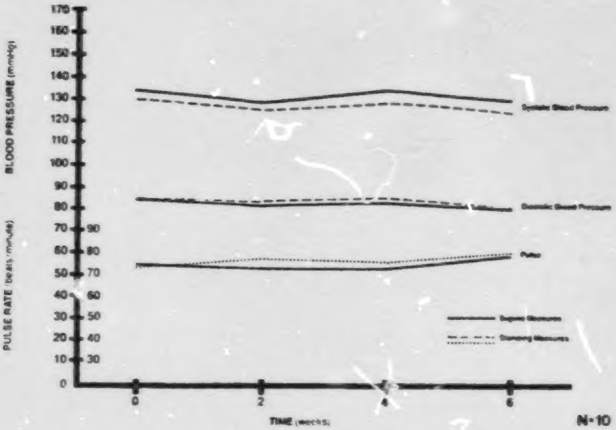
Table 2 lists the mean and range values for blood pressure and pulse values at baseline and at end of each treatment period. Figure 1 displays these values graphically.

No statistically significant differences were found between baseline values and end of treatment values for blood pressure or pulse measurements.

TABLE 2: RANGE VALUES OF BLOOD PRESSURE (mmHg) & PULSE RATE DATA (beats/minute) AT THE END OF EACH TREATMENT PERIOD (Mean Values Within Parenthesis) N=10

MEASUREMENT	BASELINE	WEEK 2 (25mg PPA) 100 mg caffeine	WEEK 4 (Placebo)	WEEK 6 (75 mg. PPA)
Standing Pulse	54-88 (73.0)	64-96 (76.4)	56-88 (75.8)	50-98 (80.0)
Supine Pulse	54-92 (73.3)	56-88 (72.5)	56-84 (73.6)	64-96 (76.2)
Standing Diastolic	74-92 (84.2)	70-94 (82.0)	70-90 (82.2)	64-92 (80.2)
Supine Diastolic	70-94 (83.4)	60-90 (80.0)	62-90 (81.2)	60-90 (79.6)
Standing Systolic	116-142 (130.6)	100-166 (125.2)	114-148 (127.8)	100-158 (124.2)
Supine Systolic	114-170 (133.3)	108-164 (127.8)	112-150 (132.4)	90-150 (129.6)

Figure 1. MEAN BLOOD PRESSURE (mmHg) AND PULSE RATE (beats/minute) VALUES AT BASELINE AND END OF TREATMENT WEEKS.



VI. STUDY RESULTS

:. Blood Pressure and Pulse Rate Data (continued)

b. Baseline vs ½, 1, 2, and 4 Hour Values

Table 3 lists the means and the range of values for blood pressure and pulse measurements at baseline and at ½, 1, 2 and 4 hours following the first medication dosage for all three treatment groups. Figures 2 through 4 display the means of these values graphically.

No clinically significant differences were found between the mean blood pressure and pulse values at baseline, and ½, 1, 2 and 4 hours following the first medication dosage, although eleven statistically significant differences were seen. Clinical insignificance is easily determined by examining (a) the small changes between baseline values and (b) the small differences between "textbook" values for normotensive patients (diastolic blood pressure, 60-90 mmHg; systolic blood pressure, 100-140 mmHg; pulse, 70-90 mgHg) and treatment values.

TABLE 3 RANGE VALUES OF BLOOD PRESSURE (mmHg) & PULSE RATE (beats/minute) DATA AT ½, 1, 2 and 4 HOURS AFTER MEDICATION
N=18
(mean values within parenthesis)

MEASUREMENT	BASELINE	½ HOUR AFTER MEDICATION	1 HOUR AFTER MEDICATION	2 HOURS AFTER MEDICATION	4 HOURS AFTER MEDICATION
		WEEK 1-2 (25 mg PPA, 100 mg Caffeine, t.i.d.)			
STANDING PULSE	56-88 (73.0)	58-88 (75.2)	60-96 (76.0)	56-100 (84.2)*	56-96 (80.6)
SUPINE PULSE	56-92 (73.3)	52-84 (69.6)	52-88 (68.[illegible])	72-96 (76.[illegible])	64-96 (76.0)
STANDING DIASTOLIC	74-92 (84.2)	70-94 (87.0)	80-100 (86.6)*	70-96 (85.9)	74-94 (85.6)
SUPINE DIASTOLIC	70-94 (83.4)	68-96 (85.0)	84-100 (88.0)*	80-98 (87.5)	70-98 (87.8)
STANDING SYSTOLIC	110-142 (130.6)	126-152 (135.6)	110-150 (134.2)	110-160 (137.2)*	110-150 (136.0)
SUPINE SYSTOLIC	114-170 (133.5)	118-172 (136.0)	138-190 (145.4)*	130-170 (143.2)*	116-160 (142.4)*
			WEEK 3-4 (PLACEBO)		
STANDING PULSE	64-96 (76.4)	64-96 (78.4)	58-100 (78.8)	72-100 (82.0)*	60-96 (79.0)
SUPINE PULSE	56-88 (72.5)	56-92 (72.6)	56-96 (71.0)	56-88 (74.8)	50-88 (73.8)
STANDING DIASTOLIC	70-94 (82.0)	58-94 (81.3)	62-100 (82.8)	56-92 (77.0)	58-90 (77.8)
SUPINE DIASTOLIC	60-90 (80.0)	50-94 (79.6)	76-94 (82.4)	56-90 (78.8)	60-92 (78.0)
STANDING SYSTOLIC	100-166 (125.2)	86-144 (120.4)	90-158 (119.0)	92-160 (116.6)*	96-140 (121.4)
SUPINE SYSTOLIC	108-164 (127.8)	104-172 (125.0)	150-152 (123.6)	90-158 (124.8)	108-160 (128.4)
			WEEK 5-6 (75 mg PPA, O.D.)		
STANDING PULSE	56-88 (75.8)	58-96 (73.4)	68-96 (81.0)	76-120 (83.7)*	70-100 (88.3)
SUPINE PULSE	56-84 (73.6)	56-88 (70.0)	60-90 (75.1)	64-124 (83.6)	60-100 (78.9)
STANDING DIASTOLIC	70-90 (82.3)	70-90 (82.6)	80-94 (85.8)	74-90 (81.8)	70-90 (82.7)
SUPINE DIASTOLIC	62-90 (81.2)	70-90 (83.0)	76-96 (86.2)	76-90 (85.3)	70-98 (85.6)
STANDING SYSTOLIC	114-144 (126.2)	100-146 (129.0)	110-152 (137.8)*	110-142 (127.6)	110-150 (134.0)
SUPINE SYSTOLIC	112-150 (132.4)	110-146 (135.4)	106-160 (139.6)	120-160 (137.4)	106-166 (136.0)

* Statistical Significant Differences ($p<0.05$)

Figure 2. MEAN BLOOD PRESSURE (mmHg) AND PULSE RATE (beats/minute) VALUES FOLLOWING TREATMENT ONE (25mg PPA, 100mg caffeine, tid).

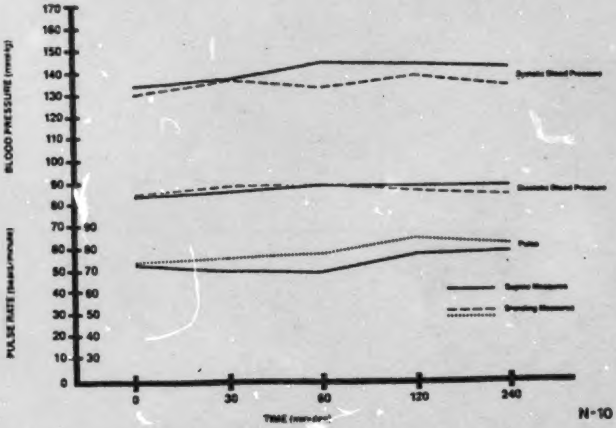


Figure 3. MEAN BLOOD PRESSURE (mmHg) AND PULSE RATE (beats/minute) VALUES FOLLOWING TREATMENT TWO (placebo).

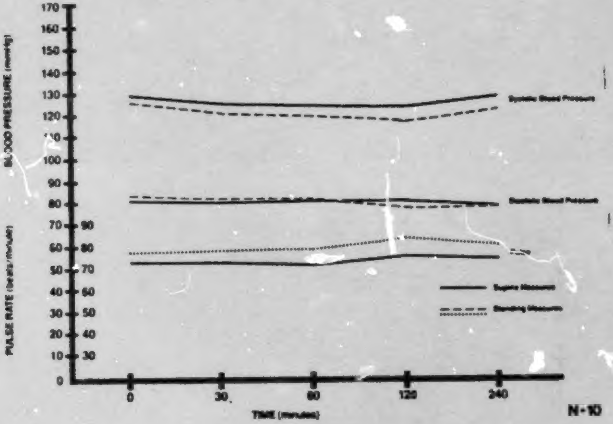
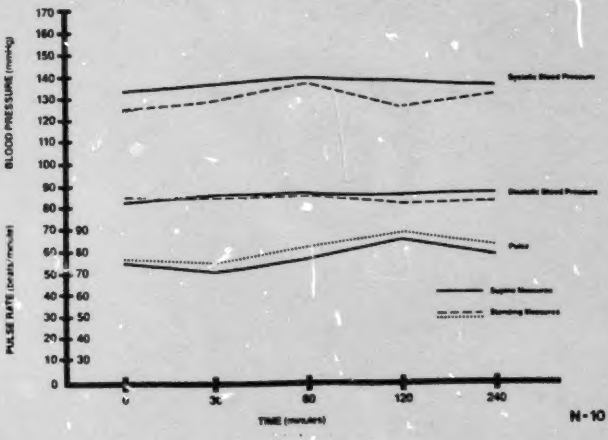


Figure 4. MEAN BLOOD PRESSURE (mmHg) AND PULSE RATE (beats/minute) VALUES FOLLOWING TREATMENT THREE (75mg PPA, OD)



VI. STUDY RESULTS

1. Blood Pressure and Pulse Data (continued)

c. Intraweekly Treatment Comparisons

No significant differences were found between any blood pressure or pulse measurements within treatment weeks in all three treatment groups, as shown in Table 5.

TABLE 5: MEAN BLOOD PRESSURE (mmHg) AND PULSE (beats/minute) BASELINE AND INTRATREATMENT WEEK VALUES (n=10)

	TREATMENT 1 (25 mg PPA, 100 mg caffeine, t.i.d.)		TREATMENT 2 (Placebo)		TREATMENT 3 (75 mg PPA, od)	
BLOOD PRESSURE	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6
Diastolic (Standing)	85.2	82.0	84.2	82.2	81.4	80.2
Diastolic (Supine)	83.6	80.0	80.9	81.2	83.4	79.6
Systolic (Standing)	137.4	125.2	128.0	126.2	127.2	124.2
Systolic (Supine)	136.8	127.8	134.0	132.4	135.8	129.6
PULSE						
Pulse (Standing)	78.6	76.4	76.6	75.8	78.5	80.0
Pulse (Supine)	73.6	72.5	73.8	73.6	73.6	76.2

2. Laboratory Blood Analysis Data

a. Baseline vs Biweekly Treatment Values

No significant differences were found between any laboratory variables for all study treatments. These results are presented in Table 6.

TABLE 6: MEAN LABORATORY VALUES FOR BASELINE AND BIWEEKLY TREATMENT VALUES (n=10)

LABORATORY TEST	NORMAL RANGE	BASELINE	TREATMENT 1 (25mg PPA, 100mg Caffeine, tid)	TREATMENT 2 (Placebo)	TREATMENT 3 (75mg PPA, od)
Glucose (mg/dl)	65-110	104.7	108.0	106.2	100.7
Triglycerides (mg/dl)	74-142	208.5	172.9	194.5	176.0
Cholesterol (mg/dl)	150-300	241.5	249.1	254.5	245.0
GGTP (u/l)	7-33	47.6	20.8	17.0	20.0
SGOT (u/l)	10-50	26.6	27.3	26.5	21.6
LDH (u/l)	100-225	176.4	180.9	166.6	149.3
Sodium (meQ/l)	135-145	139.6	140.4	141.3	140.2
Potassium (meQ/l)	3.5-5.0	4.2	4.3	4.2	4.1
Chloride (meQ/l)	95-110	101.9	102.9	102.2	103.2

VI. STUDY RESULTS

2. Laboratory Blood Analysis Data

a. Baseline vs Biweekly Treatment Values (continued):

Table 7 lists the patients with laboratory values outside the normal range. Laboratory values which increase continually or sporadically are listed in the bottom half of the table.

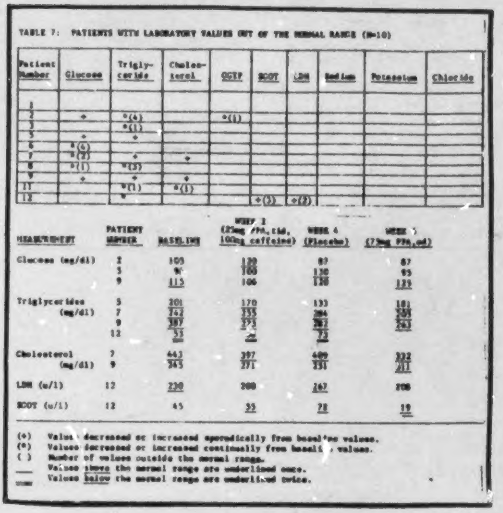


TABLE 7: PATIENTS WITH LABORATORY VALUES OUT OF THE NORMAL RANGE (N=10)

Patient Number	Glucose	Trigly-ceride	Choles-terol	GGTP	SGOT	LDH	Sodium	Potassium	Chloride
1									
2	+	*(4)		*(1)					
3		*(1)							
5	+	+							
6	*(4)								
7	*(2)	+	+						
8	*(1)	*(3)							
9	+	+	+						
11		*(1)	*(1)						
12		*			+(3)	+(2)			

MEASUREMENT	PATIENT NUMBER	BASELINE	WEEK 2 (25mg PPA,tid, 100mg caffeine)	WEEK 4 (Placebo)	WEEK 5 (75mg PPA,od)
Glucose (mg/dl)	2	105	120	87	87
	5	96	100	130	95
	9	115	106	120	125
Triglycerides (mg/dl)	5	201	170	133	181
	7	242	235	204	205
	9	387	273	282	263
	12	33	[illegible]	73	
Cholesterol (mg/dl)	7	443	397	409	332
	9	265	271	231	211
LDH (u/l)	12	230	200	267	208
SGOT (u/l)	12	45	35	78	19

(+) Values decreased or increased sporadically from baseline values.
(*) Values decreased or increased continually from baseline values.
( ) Number of values outside the normal range.
— Values above the normal range are underlined once.
═ Values below the normal range are underlined twice.

VI. STUDY RESULTS

2. Laboratory Blood Analysis Data (continued):

b. Biweekly Laboratory Values

With the exception of one instance, statistical comparisons of lab values between treatment one, two and three showed no significant differences. The exception occurred between treatment one (25mg PPA, 100mg caffeine, tid) and treatment three (75mg PPA, od) glucose levels. At week 2, the mean glucose value was 108.0mg/dl and at week 6 the mean glucose value had decreased to 99.4mg/dl ($p<.05$), a change of 8.6mg/dl.

3. Oral Temperature Values

Oral temperature values did not fluctuate. All temperature values were 98.6.

C. WEIGHT LOSS DATA (Efficacy Analysis)

Patients receiving phenylpropanolamine lost more than 1 pound per treatment week as shown in Table 8.

TABLE 8: MEAN CUMULATIVE WEIGHT LOSS/WEEK (lbs)

TREATMENT	WEIGHT LOSS
25mg PPA (tid)	-1.9
75mg PPA (od)	-1.6
Placebo	-0.63

These values exceed the FDA finding of a mean weight loss of 1 pound per week among 10,000 patients receiving prescription weight loss aids.

Ninety-three percent (93%) of the patients reported that they experienced none or slight hunger feelings after receiving 25mg PPA (tid), or 75mg PPA (od). Seventy-one percent (71%) of the patients reported that they experienced moderate or marked hunger feelings after receiving treatment 2 (placebo).

D. SIDE EFFECTS

One patient (#7) reported feeling nausea and dizziness during the first week of medication (25mg PPA, t.i.d.).

VII. CONCLUSIONS

The lack of clinically significant differences between baseline and ¼, 1, 2 and 4 hour blood pressure and pulse values provides safety data for the use of phenylpropanolamine appetite suppressant products by stable, controlled hypertensive patient populations. In addition, differences between baseline and end of treatment values showed non-significant differences for all comparisons plus intraweekly treatment comparisons showed no significant differences. These results justify the continuation of this pilot study.

The effectiveness of phenylpropanolamine appetite suppressant aids for stable, hypertensive populations was also substantiated in this pilot study. The patients receiving 25mg (tid)* and 75 mg (od) showed a mean weight loss of 1.9 pounds and 1.4 pounds per week, respectively, which exceeds the FDA finding of a mean weight loss of 1.0 pounds per week for 10,000 patients receiving prescription weight loss aids, as presented in the "Review of Amphetamine-Like Drugs by the FBD" in Obesity in Perspective (Vol II, Part II, Bray, GA, ed. Washington, DC, Government Printing Office, 1976, pp.441-443). The incidence of reduced hunger feeling (86%) was greater among patients receiving active medication.

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*plus 100mg caffeine.

THE PROPRIETARY ASSOCIATION
1700 Pennsylvania Avenue, N.W./Washington, D.C. 20006/Phone (202) 393-1700

August 27, 1982

Arthur Hull Hayes, Jr., M.D.
Commissioner of Food and Drugs
Dockets Management Branch (HFA-305)
Room 4-62
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Reply Comments: Weight Control Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Advance Notice of Proposed Rulemaking, 47 Fed. Reg. 8466 et seq. (February 26, 1982), Docket No. 81N-0022

Dear Sir:

Comments were due on July 26, 1982, on the above proposal, which consists of a Report and Proposed Monograph of the Advisory Panel on OTC Miscellaneous Internal Drug Products, convened by the Food and Drug Administration under its OTC Drug Review. Reply comments were to be submitted by August 27, 1982

These reply comments are filed on behalf of The Proprietary Association, a 101-year-old trade association, the active members of which are engaged in the manufacture and distribution of nonprescription or over-the-counter medicinal products. Members of the Association are subject to the Federal Food, Drug and Cosmetic Act (21 U.S.C. 301, et seq.) and are interested in and affected by this proposal.

These reply comments are not intended to supersede any which may be filed by individual members of the Association.

Comments Which Assert that Phenylpropanolamine Causes High Blood Pressure or Other Adverse Reactions.

The principal concerns of the Center for Science in the Public Interest (CSPI) regarding the safety of phenylpropanolamine rest on what CSPI describes as "the known tendency of PPA to raise blood pressure...." (CSPI, p. 5.) To the contrary, there have been no studies submitted or cited by any participant in this proceeding that support the proposition that PPA has a "known tendency" to raise blood pressure at the dosage levels recommended in the ANPR.

In its discussion of the relationship between PPA and hypertension, CSPI states that after the Panel's report on weight control products containing PPA was submitted to FDA in 1979 "several reports of alarming cardiovascular reactions to recommended quantities of PPA appeared in the the medical literature." (CSPI, p. 6.) "In response to this evidence," CSPI goes on to state, "FDA took regulatory action to remove from the market all weight control products containing single, immediate-release doses of greater than 37.5 mg of PPA and timed-release doses of greater than 75 mg." (CSPI, p. 6.) This is incorrect. In actuality the action by FDA to limit products to single, immediate-release doses of not greater than 37.5 mg of PPA and timed-release doses of not greater than 75 mg was based on the agency's position that products which contained higher doses were not marketed OTC prior to December 5, 1975, and were, therefore, "new drugs." (47 Fed. Reg. 8468, February 26, 1982.)

CSPI cites the double-blind trial reported by Horowitz, et al., in 1980 as substantiation for its assertion that the available evidence does not support a Category I classification for any dose of PPA. The Association commented extensively on the Horowitz study (see p. 5 of PA Comments), and now wishes to add that the study by C. A. Mitchell, referred to on page 7 of our comments, did not report comparable results with the 50 mg timed-release portion of the study. In a cross-over study, six normotensive volunteers received placebo or 50 mg PPA plus 0.25 mg belladonna alkaloids. Blood pressure and pulse were recorded every 15 minutes for the first [illegible] minutes and every 30 minutes for the next 90 minutes after dosing. Mitchell reported no statistically significant differences between drug and placebo on mean arterial pressure or pulse.

Nor did 11 percent of those persons who received 50 mg of PPA in a timed-release form in the Horowitz study develop "significant, sometimes severe diastolic hypertension," as CSPI asserts. (CSPI, p. 6.) Horowitz reported that four of the 37 subjects had a diastolic reading of 100 or more, and reported that one of those four participants had a maximum supine blood pressure of 145/110 mm Hg. Presumably the subject with the 145/110 mm Hg. reading had the highest diastolic reading of the four subjects with readings of 100 or more. This is not equivalent, however, to reporting that the subjects had "severe diastolic hypertension," as CSPI states, nor did Horowitz so classify those subjects. Moreover, although Horowitz stated that three subjects in the 85 mg portion of the study received anti-hypertension therapy, he did not report that any of the subjects in the 50 mg portion of the study received anti-hypertension therapy.

CSPI further asserts that one would expect the elevated diastolic blood pressure readings reported in the subjects in the Horowitz study who received a 50 mg timed-release capsule to occur in more people if a 75 mg dose were ingested. (CSPI, p. 7.) In fact, the Noble study cited on page 7 of our comments demonstrates that no such result occurred.

The speculations of CSPI are further negated by the fact that in 1981 approximately five billion doses of PPA were taken in the form of cough/cold and weight control OTC products, with only a handful of reports of adverse reactions, which appear to be either idiosyncratic or due to overdoses.

The comments of the California Association of Neurological Surgeons, Inc. and those of Arthur F. Shinn, Pharm. D., Beecham Laboratories, raise a similar safety concern when PPA is ingested. However, the reports cited in those comments simply do not indicate that there is a relationship between PPA and the reactions reported when PPA is ingested at the dose levels recommended in the ANPR. The comments of the California Association of Neurological Surgeons, for example, report three cases of adverse reactions after ingestion of PPA. Case 1 and Case 2 are, respectively, a report of an overdose of an OTC weight-control product, and a report of ingestion of an illegal "look-alike" product. Case 3 is a report of an adverse reaction after the ingestion of an OTC "diet pill," which is not otherwise identified. As to Case 3, it should also be noted that the report states that vomiting occurred immediately after ingestion and that the adverse reaction occurred after the vomiting. It is unlikely, therefore, that the adverse reaction resulted from the ingestion of the "diet pill."

Similarly, the reports cited by Shinn involved overdoses, ideosyncratic reactions and/or illegal combinations. Case 1 involved a patient with a history of epilepsy who had a seizure apparently coincidentally with the ingestion of two combination cough/cold products. In Case 2 the patient had consumed three to five ounces of whiskey just prior to ingesting two "black capsules," each containing a combination of 200 mg caffeine, 25 mg ephedrine and 50 mg PPA, a combination which FDA has since declared to be an unapproved "new drug." (47 Fed. Reg. 35344, August 13, 1982.) Case 3 again involved two "black capsules" containing the same illegal combination.

CSPI asserts that the recommended label warning is inconspicuous and inadequate to protect persons who have hypertension, heart disease, diabetes or thyroid disease from ingesting weight control products containing PPA. (CSPI, pp. 12-13.) As an examination of the label warnings on these products shows, the warning is clear and conspicuous, as, indeed, Section 502(c) of the Act and FDA's regulations require it to be.

CSPI further asserts that "[c]onsumers have an understandable tendency to believe that drugs available on an OTC basis are safe for most potential purchases,....." (CSPI, pp. 12-13.) We believe that this is true and that it is also fully consistent with the philosophy of making medication available to the consumer on an over-the-counter basis. In stating that consumers do not read labels because they believe that OTC medicines are unqualifiedly safe for everyone, CSPI is not really questioning the safety of PPA as an OTC; it is really questioning the fundamental principle of self-medication itself -- that people are capable of using an OTC safely and effectively if they follow labeling directions.

Comments Which Assert that Phenylpropanolamine is Unsafe Because of Alleged CNS Effects

CSPI states that PPA is unsafe for use in weight control products because of reports of adverse CNS effects resulting from the ingestion of PPA. CSPI concedes that "[n]one of these incidents proves definitively that PPA can cause mental derangement," but contends that "the structural similarity is there..." between PPA and the amphetamines, adrenaline, and related sympathomimetic amines. (CSPI, p.3.) CSPI couples the structural similarity with case reports in the United States and other countries linking PPA with adverse CNS effects. CSPI cites several reports, including the Dietz survey listed in the preamble to the ANPR as Reference 9, as support for the proposition that there have been "scattered accounts that even normal doses of PPA may sometimes cause or aggravate psychotic episodes, hallucinations, or other severe behavioral aberrations that mimic amphetamine reactions." (CSPI, p.3.) We submit that the Dietz survey does not support the proposition that there are adverse CNS effects associated with the use of PPA at the dosage levels of the products currently marketed or the dosage levels proposed by the Panel. As CSPI points out, the Dietz survey is composed of scattered accounts. (CSPI, p. 3.) In addition, the seven cases referred to in the Dietz survey, which were taken from record cards of patients in emergency rooms, are accounts of isolated cases of individual adverse reactions. There was no possibility of verification of the actual doses of PPA taken since the PPA was not taken under controlled conditions, and there was no follow-up to determine whether the symptoms reported were repeated under the same or different circumstances.

The other reports cited by CSPI (CSPI, p.3, fn. 9) also fail to support the proposition for which CSPI cites them. With regard to the Achor and Extein report of precipitation of bipolar affective disorder in three patients who had been taking diet-aid products containing PPA, one patient had been taking twice the recommended dose, and the dosage for the other two patients was not reported. Therefore, one of the cases clearly involved an overdose, and the remaining two cases may have as well. Furthermore, according to the report, all three patients had histories of mood disorders. Finally, the report did not describe the patients' psychiatric status immediately prior to taking the diet aids, or after they were withdrawn. It is therefore impossible to evaluate whether PPA played any role in the psychiatric episodes reported.

The Schaffer and Pauli report cited by CSPI involved one patient who ingested three to five pills each day from two *separate* bottles of diet pills. Obviously, the reaction of that patient is of no use in any evaluation of PPA.

The report by Norvenius, *et al.*, cited by CSPI, dealt with complaints to the Swedish Adverse Drug Reaction Committee. It is unclear from the report whether the total number of complaints was 61 or 66. In any event, five patients were reported to have had psychotic episodes, but the report does not give dose levels for any of the patients. Since 48 of the patients were under age 16, it is probable that many of these patients ingested accidental overdoses. Moreover, the report specifically notes that one 17-year-old male had taken "large" quantities of a PPA and brompheniramine combination product. In view of the absence of data on the precise dosage ingested in each case, the report essentially has no probative value.

The Wharton report relied upon by CSPI describes a psychotic episode in a patient taking a cold medication containing 12.5 mg of PPA, phenyltoxolamine, phenacetin and thonzylamine. He exhibited paranoid psychosis after an eight-day period in which he had ingested 30 tablets. He was treated for the paranoid psychosis, but eight weeks after recovery he suffered a similar reaction, although he was not taking the cold medication at the time. Therefore, the psychotic reaction apparently did not result from the ingestion of PPA.

Finally, CSPI cites the Kane and Greene report of three patients who took nasal decongestants containing PPA. The reaction of two of the three patients simply does not support the Center's position. One of the patients had previously been treated for undifferentiated schizophrenia. That patient's reaction may well have resulted not from the ingestion of PPA but from a preexisting mental condition. Another patient had used "two bottles" of the decongestant within one week. There is no indication as to the actual amount of PPA taken at any one time. Accordingly, once again, the report cannot be cited as support for any proposition concerning PPA.

To summarize, the five published reports discussed above include 13 patients who experienced psychotic episodes. Three of the patients were children 8 years old or younger, who probably ingested accidental overdoses, and one patient was a 17-year-old who reportedly had taken "large quantities" of a PPA and brompheniramine combination product. Among the remaining nine patients, one had taken more than the recomended dose; another may have taken more than the recommended dose (the only information available was that the patient took "two bottles"); one apparently took two PPA-containing preparations, but dosage was not specified; four had histories of affective illness or schizophrenia and one of these took more than the recommended dose; and one patient experienced another psychotic episode eight weeks after he had discontinued use of products containing PPA. Moreover, it should be reiterated that substantially all of the complaints reported by Norvenius, et al., were complaints of restlessness, irritability, etc. Furthermore, these reports primarily involved children 15 years old and younger and, therefore, most of the cases undoubtedly involved accidental ingestions or overdoses.

CSPI also cites another case in which alleged adverse CNS reactions occurred. (CSPI p. 7.) The case involved a 44-year-old woman who developed "confusion [and] grand mal seizures" approximately an hour after taking a 75 mg timed-release weight control capsule. As a careful reading of the report of the incident indicates, the woman had previously experienced grand mal seizure reactions to cough/cold medications. Therefore, her grand mal seizure reaction was idiosyncratic. There is, moreover, no established contraindication for sympathomimetic drugs for epilepsy.

Relying on Porter & Dietsch, Inc. v. Federal Trade Commisson, 90 FTC 770 (1977), aff'd, 1979-2 Trade Cases ¶ 62,795 (7th Cir. 1979), CSPI asserts that PPA is unsafe because the advertising for weight control products containing PPA which does not include a health warning is misleading. (CSPI, p. 13). The relevancy to this proceeding of the FTC's action in that case is dubious at best. In any event, CSPI misstates the scope of the ruling in *Porter & Dietsch*. The holding was limited to the particular advertisements at issue in that case. It was not applicable to all PPA-containing weight control products. Moreover, as FDA knows, the Panel recommended a number of label warnings for these products, as discussed above.

There is an absence of any evidence establishing that adverse CNS reactions are a side effect of the ingestion of PPA at the dosage levels proposed by the Panel. In fact, the marketing experience of cough/cold and weight control products containing PPA in the United States is support for the proposition that adverse CNS reactions are not a side effect of the ingestion of PPA. Furthermore, the marketing experience is supported by a recent double-blind, cross-over study by Seppala, reported in the *British Journal of Clinical Pharmacology*. [1] The Seppala study, which also included antihistamines that provided an active control, reported no euphoric effect and an improvement in perception and reaction accuracy following ingestion of PPA at a 50 mg dose level. Seppala stated in conclusion that "[i]t is noteworthy that mood elevation...was not noted after [treatment with] phenylpropanolamine." Accordingly, in view of the results of the Seppala study, the accumulated experience from the testing and marketing of cough/cold and weight control products which fails to indicate that ingestion of PPA in the doses proposed by the Panel results in adverse CNS reactions, and the fact that the cited reports of adverse CNS reactions are either reports of ingestion of doses above the recommended dosage level or are isolated incidents, we submit that no evidence has been identified that indicates that ingestion of PPA at the recommended doses is unsafe because of possible adverse CNS reactions. We believe, therefore, that further clinical testing is unnecessary in order to evaluate the safety of PPA at the dosage levels under consideration.

CSPI, citing a letter from the British Department of Health and Social Security, states that only one PPA weight control product is marketed in Britain and that the product is a prescription drug, and implies that the FDA should adopt a similar policy with respect to weight control products containing PPA. (CSPI, p. 13.) It should be noted that Britain does permit the marketing of OTC drugs containing PPA. Menley and James markets *Contac*, its OTC cough-cold product containing PPA, in Britain.

Comments Which Assert that PPA Is Unsafe Because it is a Drug of Abuse

CSPI and G. B. Stickler, M.D., cite drug abuse as a reason for placing PPA on prescription. (SCPI, pp. 3-5; Stickler, p.2.) CSPI relies on Natonal Clearinghouse for Poison Control Center reports and Stickler, citing no sources, simply asserts that PPA "is the number one street-drug, at least in Minneapolis and probably in other cities in this country." (Stickler, p. 2.)

The Association has several comments on the points raised by CSPI and Dr. Stickler with respect to PPA and drug abuse.

(1) National Clearinghouse for Poison Control Centers (NCPCC) Data.

(a) Extrapolations of NCPCC data must be made with caution since the data are derived from only 10% of the nation's poison control centers, and the 10% are not necessarily a valid sample.

(b) The data reflect all reports of ingestions or other incidents, whether serious or not. Most of the reports discussed by CSPI with respect to PPA were made by telephone, rarely involved hospital contact and, on the average, resulted in mild, if any, side effects.

(c) As CSPI concedes (CSPI, p.5), "a large percent of the Clearinghouse PPA cases involved children ...." The Association notes that this percentage is large indeed - over 40. That is, over 40% of the cases involve children under 5 years of age. Placing an ingredient on prescription to eliminate unsupervised ingestions by children is not, the Association submits, a legal or wise measure.

As FDA knows, The Proprietary Association and its members have long been active in working to reduce unsupervised ingestions of medicines by children. The Association has participated in government-sponsored conferences and various educational activities on the subject, while its members have been experimenting with, testing, improving, and using various forms of "special packaging" since 1955. Needless to say, the Association supports CSPI's attempt to reduce accidental ingestions, including ingestions by children, of the products subject to this proposal. The Association believes, however, that attempting to combat such ingestions by placing a drug on prescription on the basis that it is "not generally recognized as safe" for OTC use is not proper.

Section 201(p) of the FDC Act defines a "new drug" as one which is "not generally recognized ...as safe and effective under the conditions prescribed, recommended, or suggested in the labeling thereof...." (Emphasis added.) In so defining the term, Congress recognized that any drug can be unsafe if used incorrectly, such as taken internally when it should be used topically and/or taken in excessive amounts. Congress therefore sought to address the question of whether a drug is safe by considering the safety of the drug in connection with the adequacy of its labeling, including its dosage recommendations, method of administration, warnings, and other precautions. Therefore, unless the labeling of the products subject to the proposal prescribes, recommends, or suggests ingestion of amounts which are toxic, such products do not meet the statutory definition of "new drug."

The Consumer Product Safety Commission (CPSC), on the other hand, has the express Congressional mandate "to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting" these and other products by requiring special packaging where appropriate. (140 U.S.C. 1472(a)(1).) Accordingly, the Association suggests that CSPI submit to CSPC what information it has on accidental ingestions of such products by children. FDA, however, is without authority to proceed against such products as "new drugs."

Nor is placing these products on prescription necessarily a useful means of protecting children from the dangers of unsupervised ingestion of drugs. Unsupervised ingestion by children is a function of the accessiblity of the drug to children and the adequacy of parental supervision, not of the legal status of the drug as prescription or OTC.

(d) The Clearinghouse data include a number of suicide gestures. The Association notes that none of the gestures succeeded. Moreover, the safety of OTCs, which are products intended to be taken according to label directions, cannot properly be judged on the basis of data regarding their use in attempted suicides.

(e) For a general but more detailed discussion of the data contained in the August, 1981 NCPCC Bulletin, the Association is enclosing as Attachment A written comments of Charles Winick, Ph.D. Dr. Winick is a Professor at the City University of New York Graduate School, co-editor of the Journal of Substance Use and Abuse, a contributing editor of the Journal of Drug Issues and Addictive Diseases, and a longtime consultant to, and principal investigator on, many projects funded by federal government agencies concerned with drug abuse.

(3) Potential for Abuse of Phenylpropanolamine

CSPI states that the Griffith, et al., study which indicated that PPA lacks abuse potential is of questionable significance. No basis for this criticism is given. The Griffith study was well-controlled and conclusively established that drug self-administration procedures with laboratory animals have provided an important conceptual and methodological focus for the pre-clinical assessment of abuse potential. In this study, conducted at Johns Hopkins University, a quantitative ratio measure was developed which permitted comparison between the reinforcing potency of either phenylethylamine anorectics and cocaine in laboratory baboons. The well-controlled study clearly demonstrated that PPA has a zero potential for abuse.[2/] Seppala confirmed this in humans, finding no mood-elevating component from 50 mg immediately available doses.[1/]

(4) "Amphetamine Look-Alikes"

(a) CSPI questions the safety of PPA for what the Center sees as the ingredient's contribution to drug abuse from the sale of "amphetamine look-alikes," described by CSPI as combinations of PPA, ephedrine, and caffeine. (CSPI, p. 3.) The Association notes that such combinations are not Category I combinations nor is anyone, to the Association's knowledge, proposing that they be placed in Category I. They are thus not relevant to discussions of PPA when used according to the terms set forth in the ANPR. Indeed, FDA has recently taken the position that such combinations are unapproved "new drugs." (47 Fed. Reg. 35344, August 13, 1982.)

(b) Since 1980, 43 states have considered and 33 have enacted legislation which prohibits trafficking in what CSPI describes as "amphetamine look-alikes." Both the U.S. Drug Enforcement Administration and the American Medical Association have developed model bills along this line. The Association understands that in states which have passed such legislation, the problems of abuse of such "look-alikes" has substantially declined. In addition, both FDA and the Post Office Department have instituted seizure actions against a number of manufacturers of such products.

(c) As noted earlier, Dr. Stickler asserts that PPA "is the number one street-drug, at least in Minneapolis, and probably in other cities in this country." (Stickler, p.2.) It appears that what Dr. Stickler is discussing is not PPA in the recommended dose but rather PPA in the illegal combinations discussed above.

Comments Which Question the Effectiveness of Phenylpropanolamine

On page 1 of its comments, CSPI states that one of its concerns regarding weight control products containing PPA is the lack of evidence to support claims of efficacy. CSPI attributes this lack of evidence to the drug manufacturers' alleged refusal "to reveal to the scientific community details of most of the studies purported to back claims of efficacy." Needless to say, all studies submitted to FDA under its OTC Drug Review on PPA are public.

CSPI also states that the Panel's conclusion that the new studies presented to it (Refs. 6 through 11) established the efficacy of such products was "qualified by the statement that 'each of these studies is defective in one or more important ways'." (CSPI, p. 15.) This statement is incorrect. The Panel concluded that PPA is effective and their finding was unanimous. What the Panel in fact stated was that:

> While each of these studies is defective *in one of (sic) more important facets covered by the Panel's proposed protocol*, the Panel believes that the combined evidence of these studies does establish the effectiveness of phenylpropanolamine hydrochloride. (47 *Fed. Reg.* 8475, February 26, 1982.)(Emphasis added.)

CSPI states that the results from the 10 double-blind studies in the public docket do not "support any claim of efficacy." (CSPI, p. 19.) To the contrary, the following data represents the weight loss achieved by patients on phenylpropanolamine and patients on placebo in eight clinical studies presented to the Panel:

Average Weight Loss Per Week

Phenylpropanolamine	1.16 lbs.
Placebo	.56 lbs.
The difference is	.60 lbs.

Moreover, several years ago FDA evaluated 210 double-blind studies in which prescription appetite suppressant products were compared against placebo. These studies represented 105 new drug applications and contained data on nearly 10,000 patients. Scoville[3], in reporting on these results, indicated that of the 4,543 patients on active drug and 3,100 patients on placebo, the weight loss averaged 0.56 pounds per week more for each patient on active drug than on placebo. The results with OTC products containing PPA compare favorably with this result. The average weight loss achieved by patients on the phenylpropanolamine program was .60 pounds *more* than the weight loss achieved by the patients on the placebo-plus-diet program. It is also important to point out that, when phenylpropanolamine was evaluated in these double-blind clinical studies against either a lactose capsule or an active prescription medication, each patient was given, in addition to medication, a 1250 calorie diet, as well as explicit directions from a physician. In other words, in each case the "placebo" was associated with a diet designed to cause loss of weight under the direction of a physician. Therefore, the amount of weight loss achieved by patients on the phenylpropanolamine program was even more significant because the PPA was being compared with another active program, that is, reduced diet and medical directions as well as placebo.

In conclusion, we submit that the cited studies are sufficient to support the efficacy claim made by the various manufacturers, as the Panel concluded.

CSPI cites the FTC decision in the Porter & Dietsch case, discussed above, as if it were a finding on the ineffectiveness of PPA for weight loss. (CSPI, p. 14.) Again, this misstates the case. The question put at issue by the complaint in Porter & Dietsch was "not whether the claims of weight loss are false but instead whether at the time they were made [Porter & Dietsch] possessed reasonable substantiation for them." Porter & Dietsch, Inc., 1976-1979 CCH FTC Complaints and Orders ¶ 21,320 at 21,329. The Commission made no finding as to the efficacy of PPA as an anorectic. Porter & Dietsch, supra at 21,331.

CSPI also asserts that weight control products containing PPA are of no long term benefit because users may regain weight when use is discontinued. OTC weight control products containing PPA are appetite-suppressants which are marketed as an adjunct to assist the motivated consumer on a diet. The products are marketed with diets that are based on a reduction in caloric intake, and the labelling states that weight control will occur only if the product is taken while caloric intake is reduced. Nor do these products claim that weight will not be regained if the person's caloric intake is increased.

Moreover, there is evidence which contradicts CSPI's assertion. Dr. Stanley Shachter, Professor of Psychology at Columbia University, recently concluded a long-term study to determine whether overweight patients continue to maintain reduced weight after a successful weight-loss program.[17] Asked about their weight histories, of 40 people who were obese at the outset, 25 reported losing at least 10 percent of their weight (an average of 34.7 pounds) and therefore becoming no longer obese (that is, within 10 percent of the average weight for their height and age), and remaining at that weight for an average of 11.2 years.

CSPI also cites the statement in the American Medical Associatioh's AMA Drug Evaluations that OTC products containing PPA are "only minimally effective." (CSPI, pp. 14-15.) This characterization has been repeated verbatim year after year, but investigation of the AMA's sources reveals that no scientific studies or proof of any sort are cited by the AMA to support this description of PPA.

Comments Which Question the Validity of the Silverman Study Cited by the Agency and by The Proprietary Association

In its critique of the Silverman study,[5] cited in the Agency's preamble and in CSPI, CSPI states that "the experimental design is flawed in so many important ways that one could have predicted in advance that no effects would be seen." (CSPI, p.9.) When analyzed, this criticism amounts to three points: that the study groups were too small and included only normal, healthy volunteers; that blood pressure values were presented as means for each subgroup, rather than individually; and that only one of the three subgroups was double-blinded. Having consulted with Dr. Silverman, the principal investigator for the cited study, the Association believes that these criticisms of the study are entirely without merit. The so-called "flaws" were all the result of a study design explicitly established in accordance with accepted clinical procedures to eliminate investigator or other bias.

Thus, the pool of 37 volunteers who received active medication was divided into three smaller subgroups at separate sites with a separate group of qualified investigators, each conducting its study independently of the other two subgroups. The total number of volunteers who received active medication was actually the same as the number of volunteers who received active medication (in an overdoes of 85 mg) in one of the Horowitz studies on which CSPI relies so heavily. In fact, CSPI characterizes that Horowitz study as "large." (CSPI, p. 6.) Similarly, the fact that the volunteers were normal, healthy adults was in accordance with accepted practice and was also true of both of the Horowitz studies.

The use of group means to report blood pressures is an acceptable biostatistical procedure.[6]

Finally, the fact that only one of the three subgroups was double-blinded is also not a "flaw" in the study. Each of the three subgroups was treated differently on this score for sound reasons. Study of one subgroup was open in order to simulate the conditions in the actual over-the-counter consumer use of the product. The study of a second group was single-blinded and the study of the third subgroup was double-blinded. The fact that all three subgroups studied under these various conditions produced no significant blood pressure effects reinforces the conclusion that at the tested dosage level, 25 mg, which is the most commonly-marketed immediate release dosage level, phenylpropanolamine produces no adverse blood pressure effects.

In conclusion, it should be noted that the Silverman study is only one of some 60 controlled clinical studies, cited by the Association in its comments, which demonstrate that phenylpropanolamine does not induce hypertension. This mass of positive data, together with almost 50 years of safe use of PPA in this country, clearly outweighs the handful of adverse reports referred to in the CSPI and other comments.

The Association appreciates the opportunity to submit these reply comments.

Sincerely,

THE PROPRIETARY ASSOCIATION

James D. Cope

James D. Cope
President

FOOTNOTES

1/ Seppala, et al., British Journal of Clinical Pharmacology, 12: 179-188, 1981.

2/ Griffith, et al., Biological Psychiatry, 13:1383, 1978.

3/ Scoville, B.A., "Review of amphetamine-like drugs by the Food and Drug Administration," Obesity in Perspective, Fogarty International Center Series on Preventive Medicine, Vol. II (Bray, G.A., ed.), U.S. Government Printing Office, Washington, D. C., 1975, pp. 441-443.

4/ "Don't Sell Habit Breakers Short," Psychology Today, August, 1982.

5/ Current Therapeutic Research, 28: 185-194, 1980.

6/ Goldstine, A., Biostatistics, MacMillan, N.Y., 1968, p. 272.

A

SOME COMMENTS ON POISON CONTROL CENTER REPORT ON PHENYLPROPANOLAMINE

August 1981

Charles Winick, Ph.D.

1. The August, 1981 Bulletin of the National Clearinghouse for Poison Control Centers carried an article on phenylpropanolamine Weight Control Products.

   For the calendar year 1979, there were a total of 144,262 reports of all substances. Of these, 739 were diet aids, of which 328 were named phenylpropanolamine products, or about ½ of 1% of the total. I obtained this breakdown from several conversations which I had with the senior author of the Poison Control Center report.

2. As someone who has worked for years in the epidemiology of substance abuse, on behalf of the National Institute of Drug Abuse and other agencies, I believe that the tone of the Poison Control Center report on phenylpropanolamine is unduly and inappropriately pessimistic. I do not believe that a valid extrapolation can be made from the actual data to the report's estimate of 10,000 phenylpropanolamine problem cases nationally.

3. The cases reported to the Poison Control Center may or may not be representative of what is actually happening nationally. For example, the country's largest Poison Control Center, in New York City, is one of the 90% of the country's Centers not reporting its experience to the national office. The 10% of the Centers reporting may not represent a valid sample of the national situation.

4. Of the 328 cases with product names, 64% involved no symptoms of any kind and the majority of the remainder did not have significant symptoms. Overall, most cases were telephone-informational communications. Only 6% involved a hospital contact. On the Poison Control Center scale from mild$^{(1)}$ to moderate$^{(2)}$ to severe$^{(3)}$, the phenylpropanolamine reports were, overall, mild$^{(1.4)}$.

5. Over two fifths of the phenylpropanolamine reports were under 5 years of age and almost one third were between 14 and 18 years of age. The former are presumed to be accidental and the latter may have been seeking a "high". If so, they would be disappointed because phenylpropanolamine is not an effective stimulant. The number of accidental cases is another reflection of the importance of the parent's role in management of medications in the home by always keeping medications unavailable to children.

   There were about 200 suicide gestures or attempts. Not only did none of these succeed but there was no fatality in the entire year from phenylpropanolamine, for any reason.

6. The report does not consider the temporary breakout or peaking noted by many epidemiologists when a substance first is employed by larger numbers of people. Because of unfamiliarity with the substance and a barrage of media publicity, when a substance first becomes widely used, there is often a sharp increase in emergency room visits, and calls, reports to poison control centers, mostly for reassurance. After a year or two, the number of such visits and reports declines. It may well be, therefore, that the 1979 reports of phenylpropanolamine incidents represent a temporary cresting which will diminish in the near future.

7. A substantial contributor to reports of problems with phenylpropanolamine is the proliferation of "look-alike" products which may include phenylpropanolamine along with other drugs. I understand that in every state which has enforced restrictions against "look-alike" drugs, there has been a uniform decline in reports of problems with phenylpropanolamine. If the state of Washington bans "look-alikes", this ban, in combination with the cresting phenomenon noted in the preceding paragraph, should lead to a sharp decline in reports of phenylpropanolamine mentions to Poison Control Centers.

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